Armed Forces College of Medicine

AFCM

Gastrointestinal and metabolism module

Clinical Integrated Cases
Session 2

Basic Science Principles for Clinical Reasoning

1- **Critical thinking**

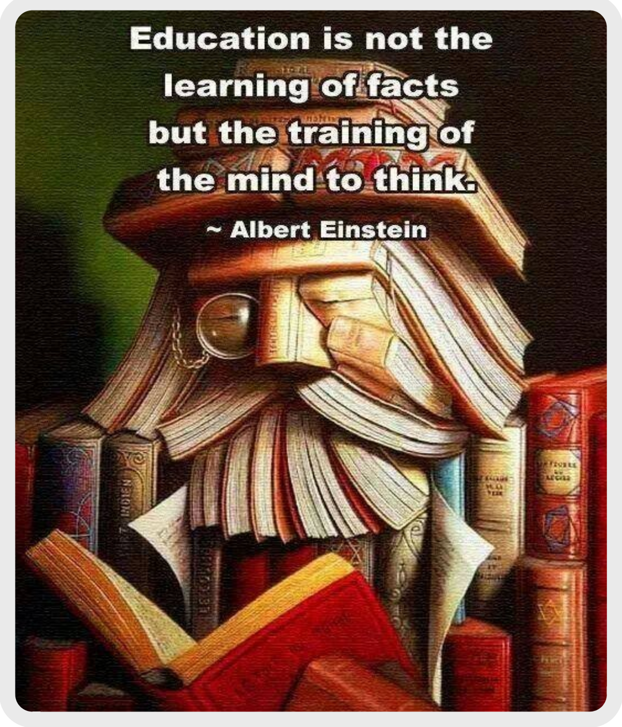
2- **Introduction to common forms of disease**

3- **Problem solving:**

Apply basic knowledge in a realistic clinical scenario.

4- **Interpersonal skills-(share and apply your knowledge)**

communication…patient


Education is not the learning of facts but the training of the mind to think.
~ Albert Einstein

Case: Diarrhea with Pain

Case coordinators

Prof. Drs. Manal Hassan Moussa, Lamiaa Foad, Yasser

Sharing departments

- **Gastroenterology department**
- **Physiology department**
- **Anatomy department**
- **Histology department**
- **Pathology department**
- **Pharmacology department**
- **Microbiology department**

Diarrhea with Pain

Mounir is 28 years male patient, engineer, single, born and lives in Alexandria, With no special habits of medical importance.

He presented with frequent passage of **blood mixed stool** for last 2 months. The frequency was about **8-10 times per day**, associated with low grade intermittent fever.

Diarrhea with Pain

Mounir also complained of **lower abdominal pain**. The pain began a few weeks ago but has become significantly worse in the past week. The patient says the pain is **crampy in nature** and located in the lower abdomen.
It does **not** radiate, and the patient can identify no specific aggravating or relieving factors

Additional symptoms include anorexia, **tenesmus**, significant **weight loss** he reported loss of 10 kg over the past 2 months.

Diarrhea with Pain

Pain in large joints (ankle, knee, and wrist) with Bilateral **painful swelling** over the chin of tibia.

Drug history:

The patient was treated several times with repeated courses of antibiotics by different physicians **without any improvement**.

- No history of upper GIT manifestations (vomiting, hurt burn or dyspepsia)
- No jaundice and no history of food allergies

Diarrhea with Pain

General examination:

Vital signs:

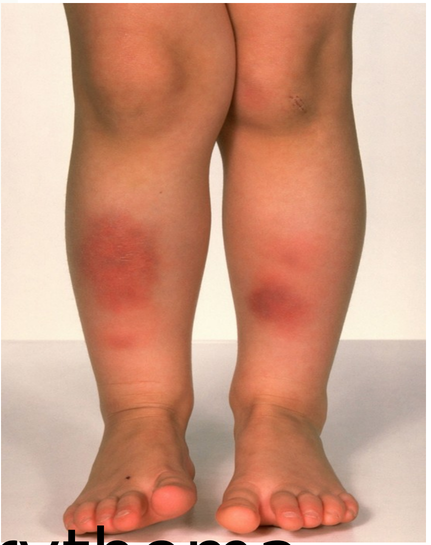
- Heart rate: 102 beats/min,
- blood pressure: 100/70 mmHg
- respiratory rate: 20/min
- Temperature: 37.3ºC

On physical examination he looked **mildly pale**

BMI: **22**

There was **no clubbing, lymphadenopathy**.

There's **bilateral tender inflammatory nodular** swelling in



Erythema nodosum

Diarrhea with Pain

Abdominal examination

- Abdomen was soft, **mild tenderness** present in lower abdomen but there was no guarding & no organomegaly.
- No abnormality was noted in the perianal region and no signs of inflammation in any joints.
- Other systemic examination revealed no abnormality

Discussion

1-a-List the patient problems

b-What is the differential diagnosis?

Inflammatory or exudative diarrhea

elevated white blood cell count, occult or frank blood or pus	
Inflammatory bowel disease	
	Ulcerative colitis
	Crohn’s disease
	Diverticulitis
Invasive infectious diseases	
	Clostridium difficile (pseudomembranous) colitis–antibiotic history
	Invasive bacterial infections (e.g., Salmonella , Shigella, tuberculosis, yersiniosis)
	Invasive parasitic infections (e.g., Entamoeba)–travel history
	Ulcerating viral infections (e.g., cytomegalovirus, herpes simplex virus)
Neoplasia	
	Lymphoma
	Colon carcinoma
	Villous adenocarcinoma

2- What are the consequences of diarrhea?

Consequences of diarrhea

1.Dehydration

2. Hypovolemic shock

3. Loss of electrolytes e.g K+

(hypokalemia)

4. Loss of HCO3 (metabolic acidosis)

5. Renal failure

3- What are the steps to be done in Mounir?

- The patient has chronic diarrhea so after **careful history** and examination the patient should undergo the **diagnostic work up of chronic diarrhea**
- Chronic diarrhea may be:

1- watery (osmotic or secretory) diarrhea

2- steatorrhea

3- inflammatory diarrhea

Ask for

- **CBC**
- **K level**
- **Serum albumin**
- **ANA**
- **Stool analysis**
- **CT abdomen**
- **Endoscopy**

Welcome Back

Diarrhea with Pain

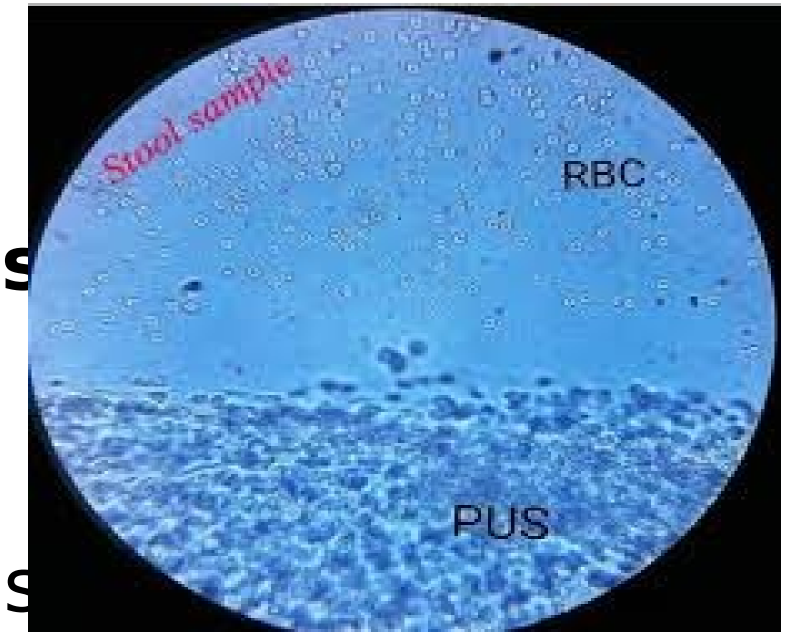
The doctor took a blood sample for CBC and electrolyte examination. Results showed:

- Hb: 9.6 g/dl
- White cell count: 8.4/cu mm with **neutrophilia** (74%)
- Platelet count: (615/cu mm).
- ESR: was 69 mm in 1st hr.
- CRP was high: 44.08 mg/dl.
- K level: 3.1 mEq/l. **Hypokalaemia**
- serum albumin: was **low** (1.9 gm/dl).
- ANA: was negative.

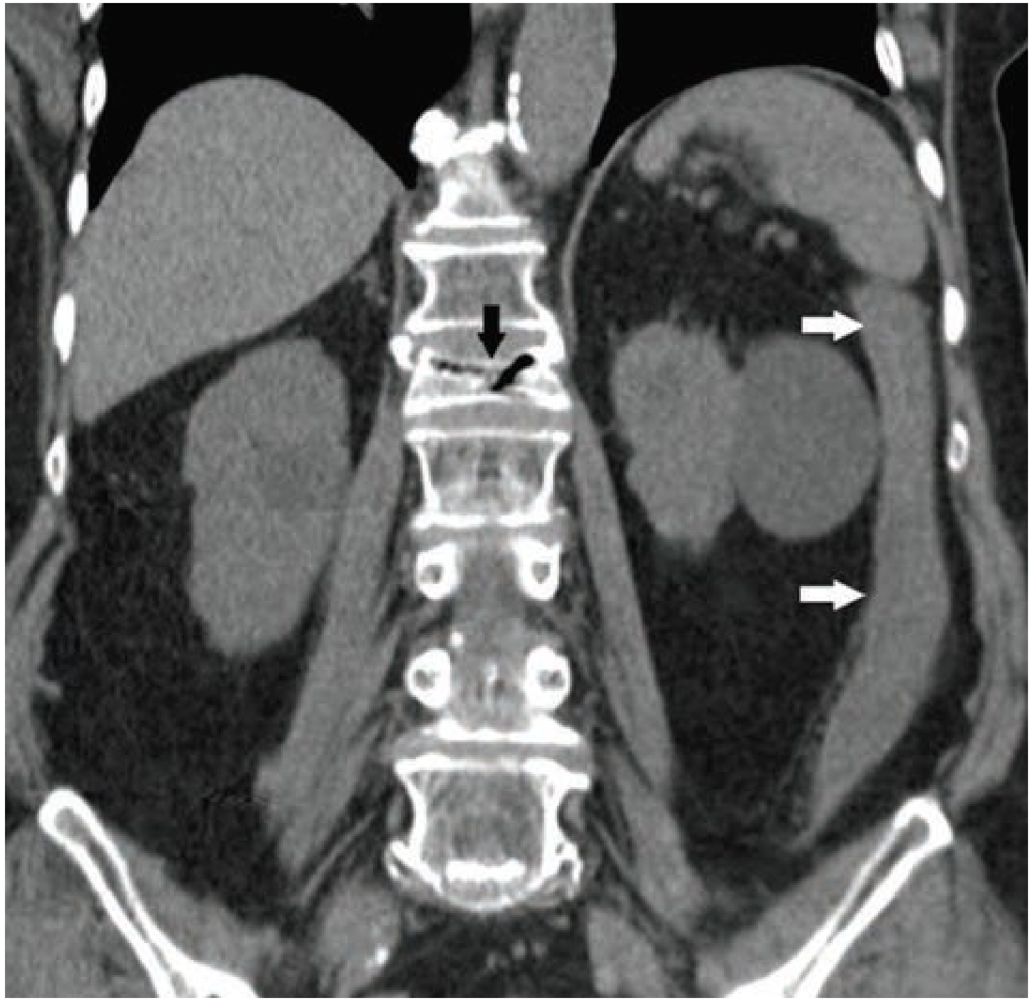
Diarrhea with Pain

Stool examination

- Stool microscopy showed numerous **pus**
- stool culture was negative.
- Abdominal ultrasound revealed normal s
- **Fecal calprotectin**: **467 µg/mg** (normal 10 – 50 µg/mg)



Diarrhea with Pain



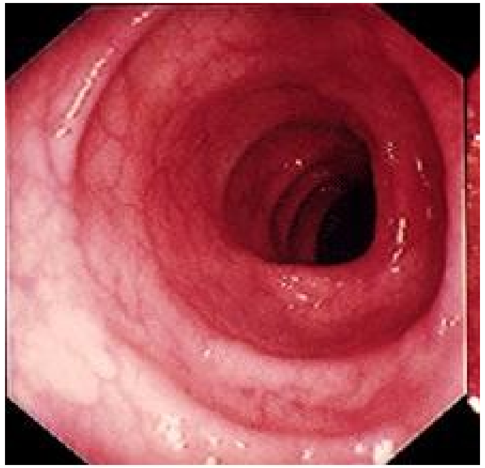
CT/MRI enterography Descending colon **shows loss of normal haustral markings of the colon** (white arrows).

Diarrhea with Pain

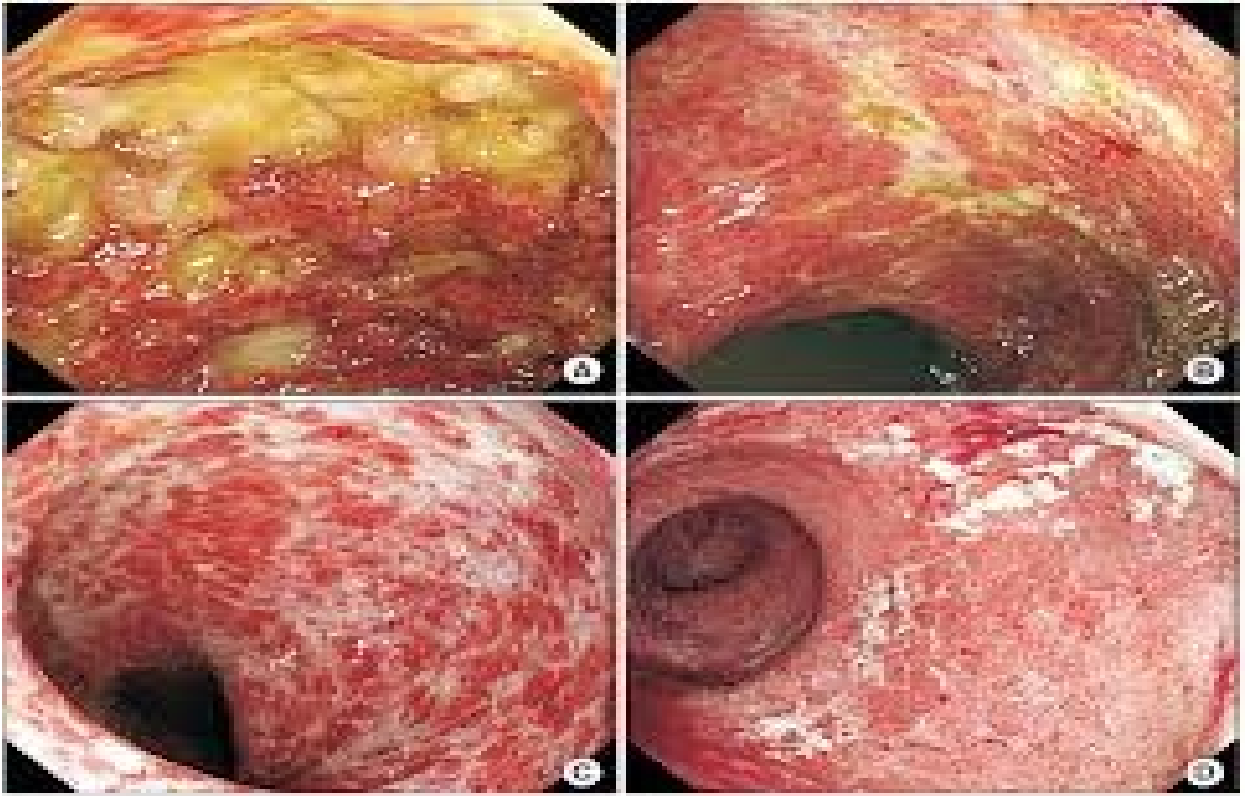
Ileo-colonoscopy was ordered. Endoscopy findings

- Granular and friable mucosa, multiple erosions and ulcerations with pseudopolyps affecting the descending colon ,not exceeding the splenic flexure **without intervening normal areas.**

Biopsies were taken for histopat



Healthy Colon

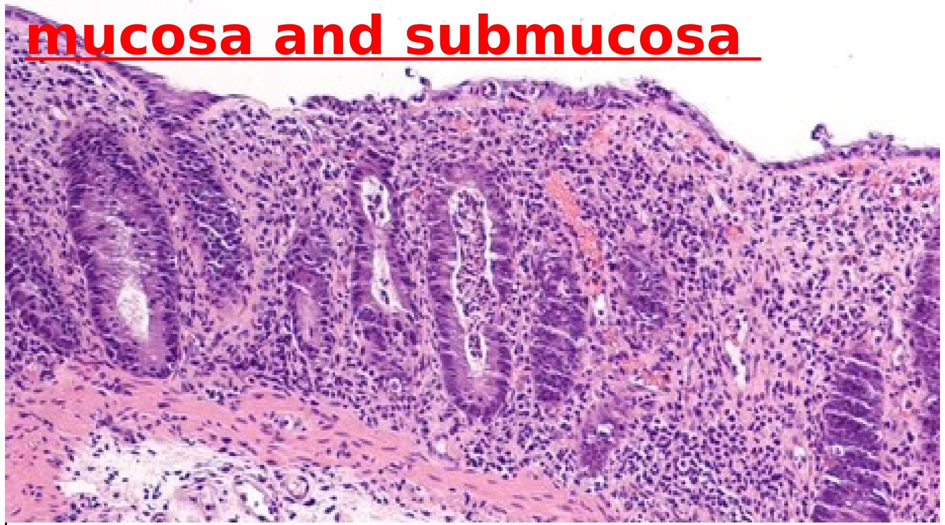


Diarrhea with Pain

Microscopic findings in the biopsy:

Pathologic features that are typically seen include ulceration, **inflammation limited to the mucosa and submucosa** formed of mixed inflammatory infiltrate, **cryptitis** , **crypt abscesses, goblet cell depletion**.

inflammation limited to the mucosa and submucosa



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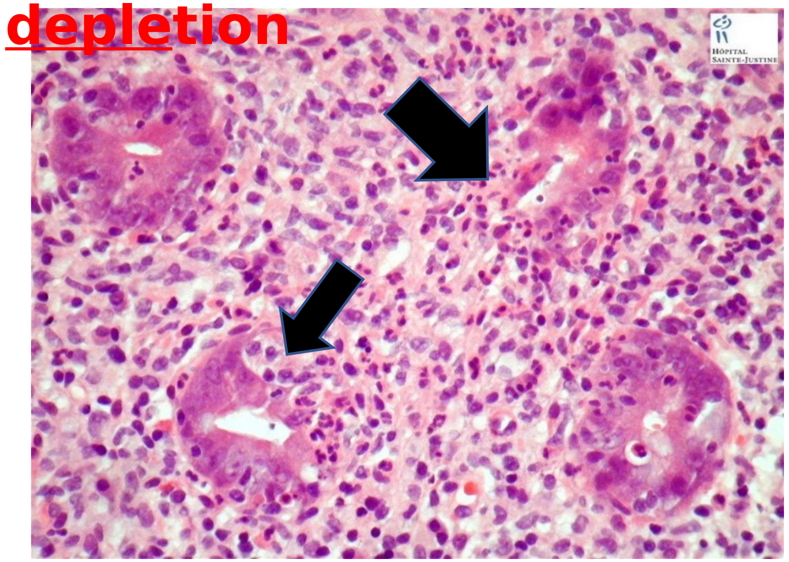
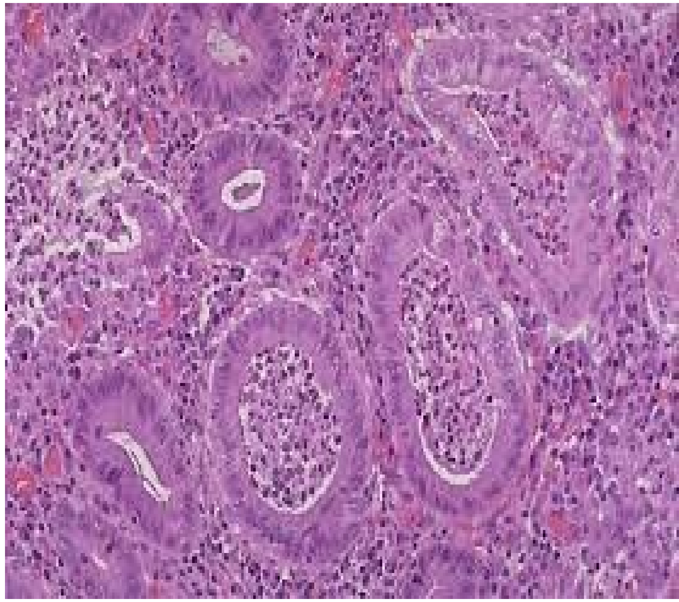
Cryptitis- goblet cell depletion



crypt abscesses,



So, what is the final diagnosis?

- A case of left sided ulcerative colitis

4- Explain the hypokalemia

- Normally K+ moves from blood to the intestinal lumen and the lumen is –ve (-50mv in colon) relative to blood. So with diarrhea (loss of ileal & colonic fluid) there will be hypokalemia.

- Also, due to enhanced K secretion through K channels in the apical membrane of colonic epithelial cells by the inflammatory process.

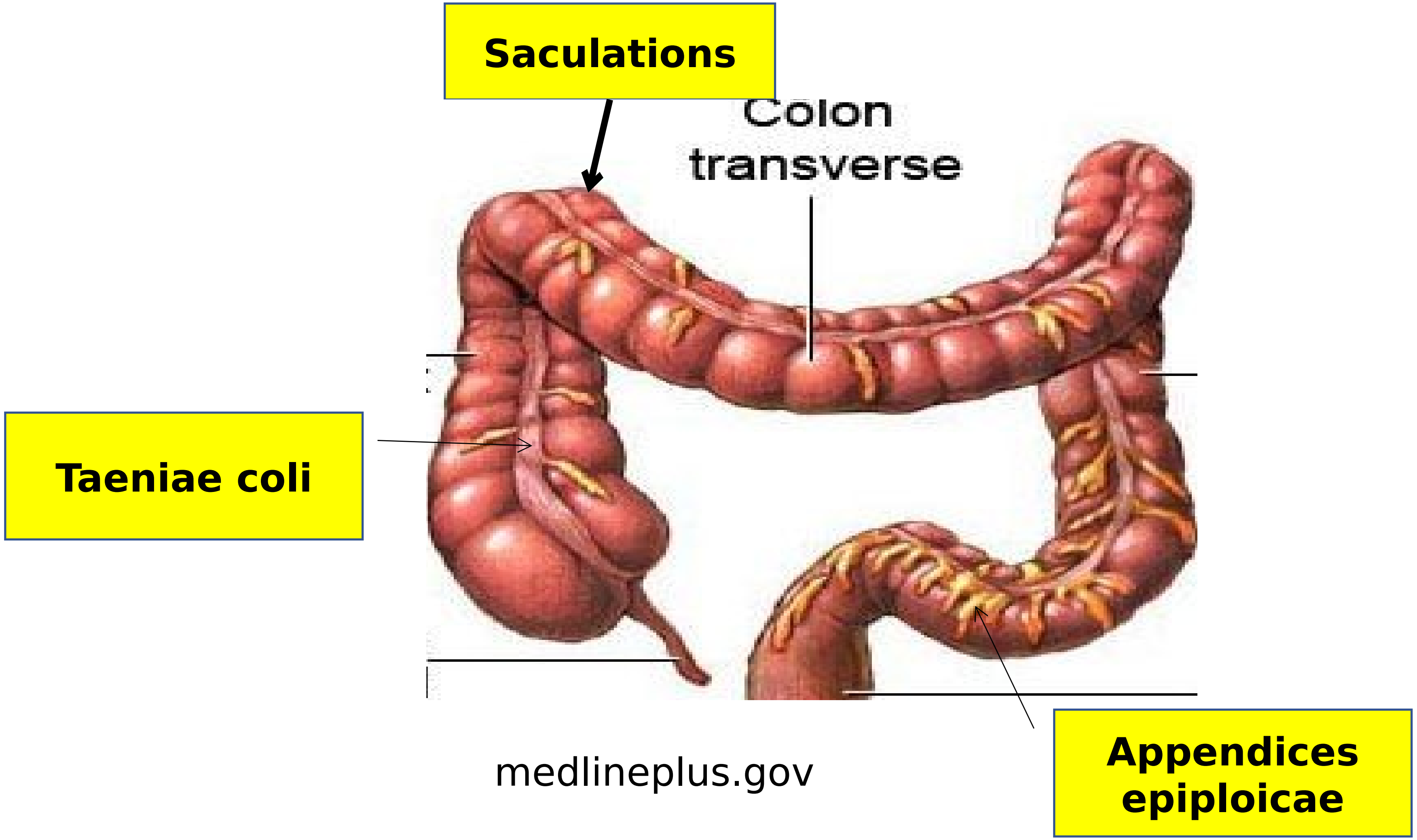
- This hypokalemia can lead to paralytic ileus as loss of intracellular K+ leads to hyperpolarization of cells with a decrease in excitability.

Descending colon showed loss of normal haustral markings of the colon

What are the characteristic features of the wall of large intestine?

The wall of the large intestine is characterized by:

- **1) Appendices epiploicae.**
- **2) Taeniae coli.**
- **3) Sacculations (haustrations).**



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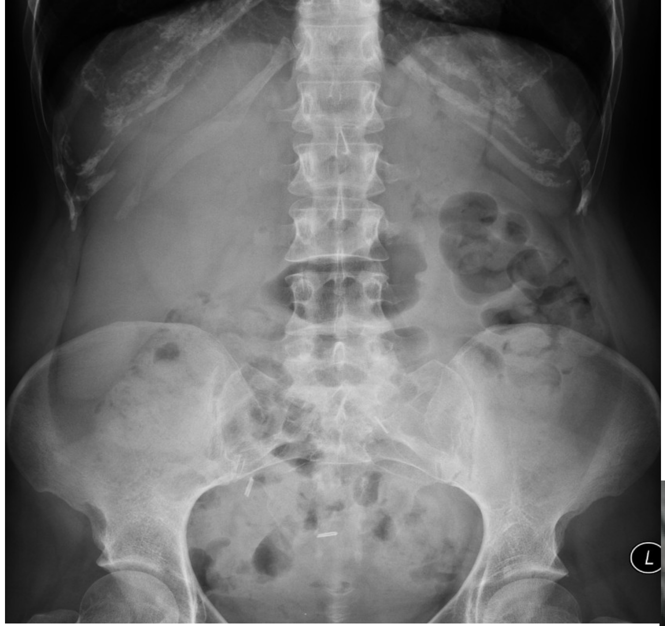
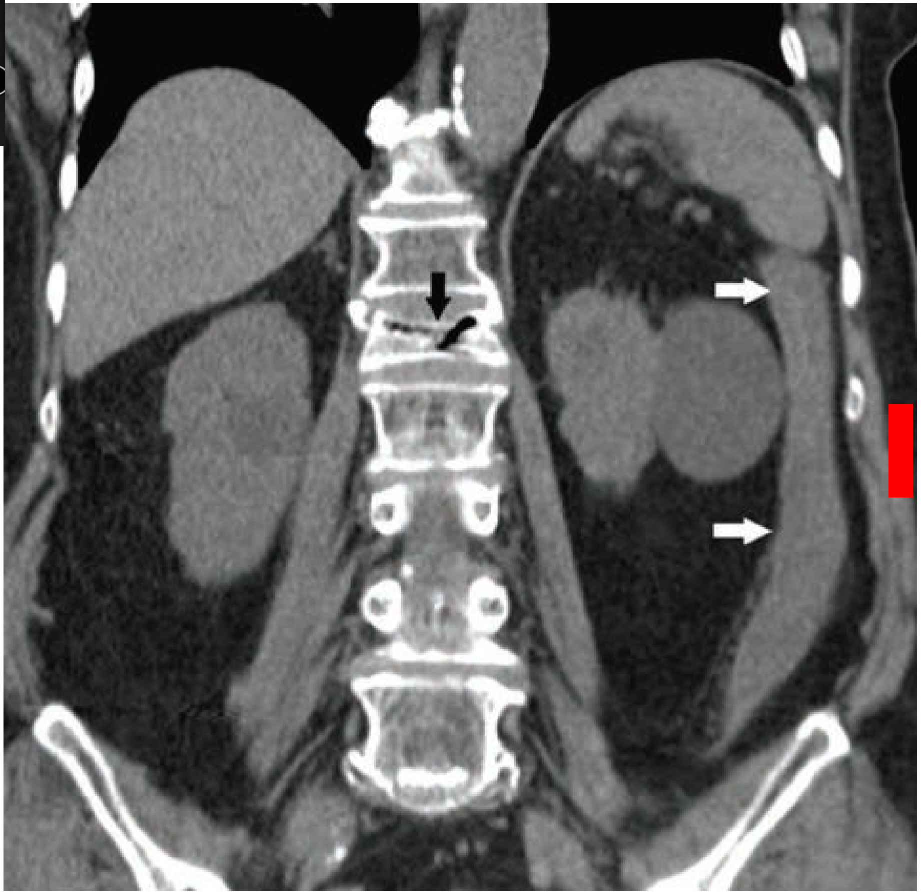




Interpret

5- What is normal microscopic structure of the descending colon?

Structure of colon

a) Epithelial lining:

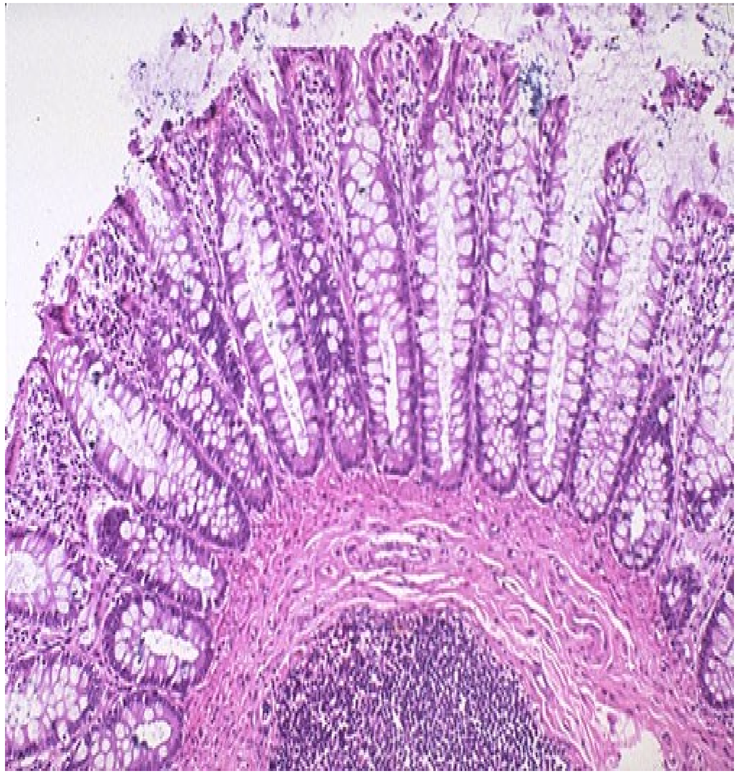
- Simple columnar epith.
- Cells as small intestine, but **NO Paneth**

- Absorptive Columnar cells (colonocytes).
- **Numerous** Goblet cells.
- Few Enteroendocrine cells.
- Stem cells: at base of the crypts

b) Lamina Propria

C.t. occupied by crypts (**G**lands) + rich in lymphatic nodules (**G**ALT).

c) Muscularis Mucosa (IC, OL).



library.med.utah.edu

2- Submucosa

- *C.t. containing **M**eissner's plexus-*
- No glands.

3- Musculosa

yenteric plexus

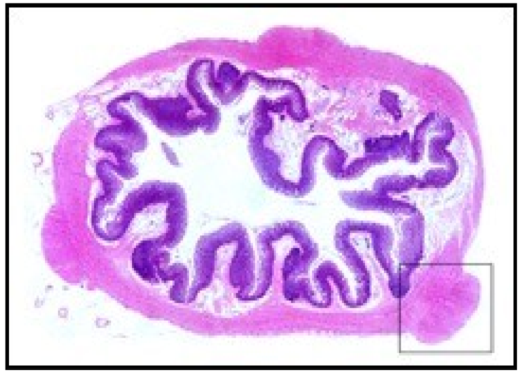
- The outer longitudinal layer is not continuous

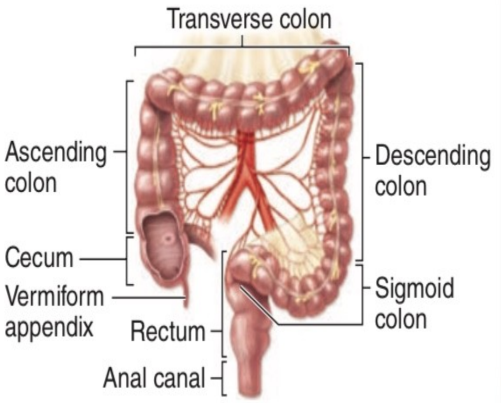
3 bundles or bands called **Taenia Coli** (ribbons of the colon)

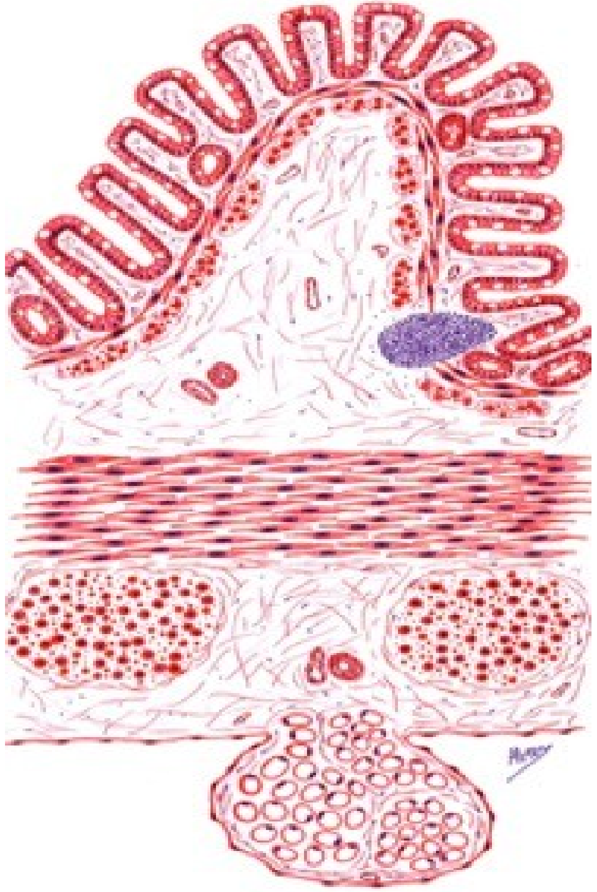
↓

make the haustra (pouches) of large intestine

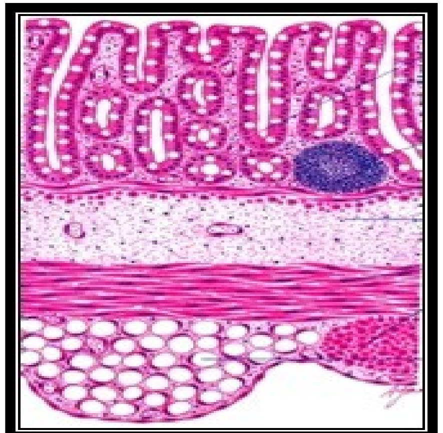
4- Serosa

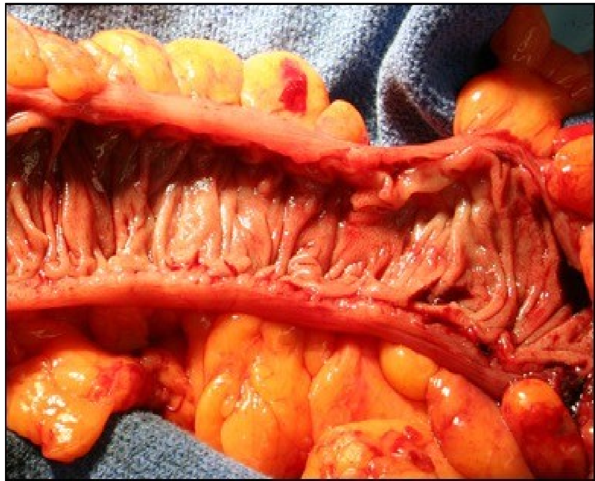






Histology department ASU





6- What are the pathological changes in the descending colon that helped to diagnose Mounir’s case?

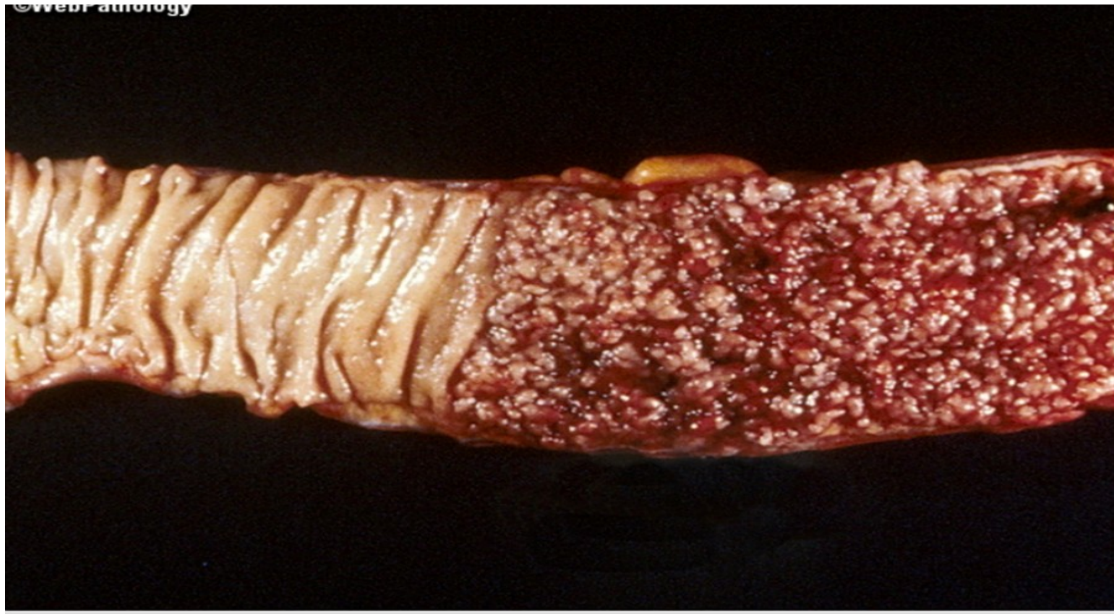
NB: **Diagnosis of IBD requires**

Clinical, endoscopic and pathologic correlation

Ulcerative Colitis

Gross:

- Mucosa:
  - Red-Granular-Friable
  - Ulcers
  - Inflammatory Pseudopolyp
  - Or atrophic &flat mucosa
  - Loss of vascular pattern
- Disease of continuity= No skip lesions (no intervening normal areas)



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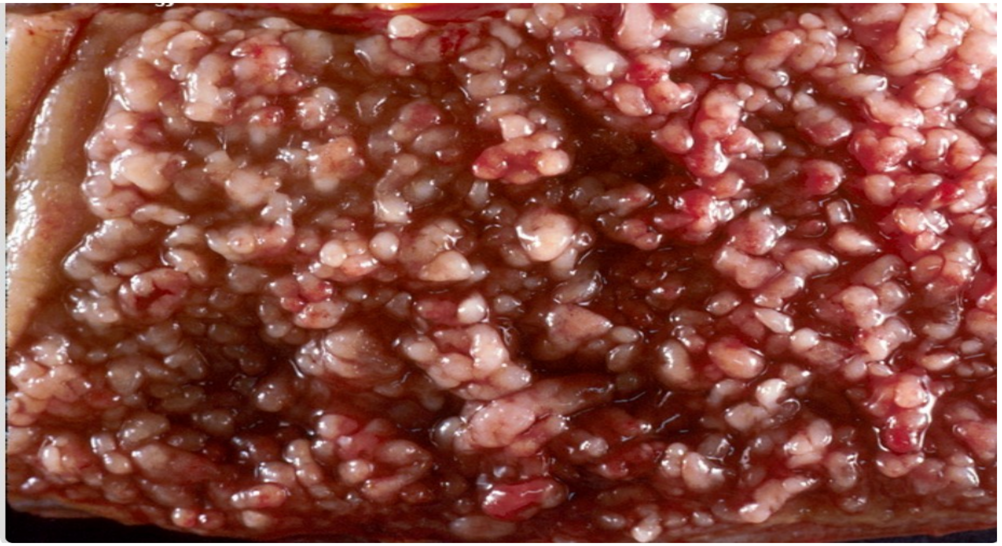

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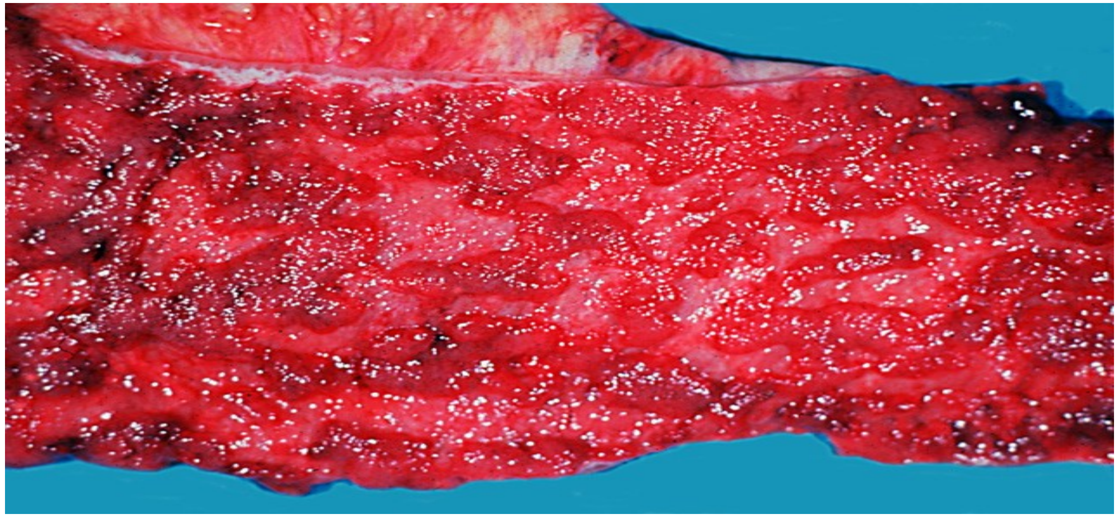

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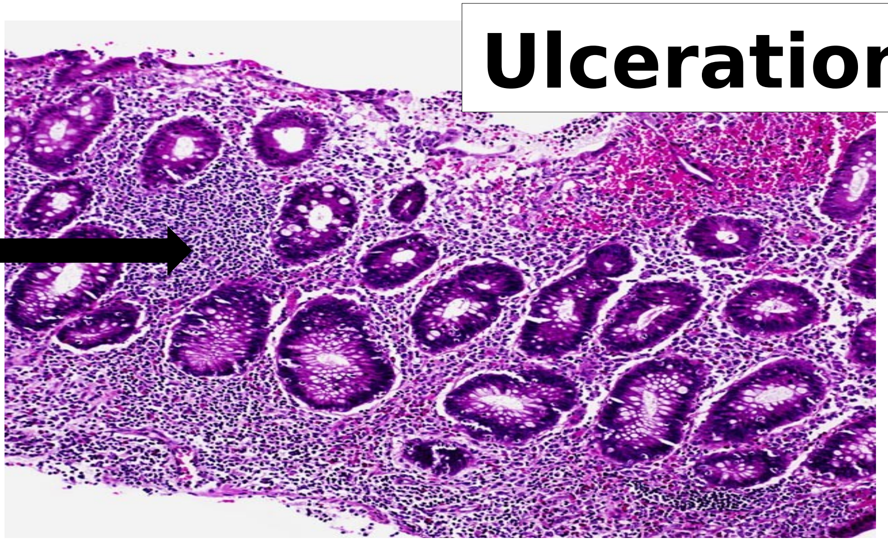
Ulcerative Colitis

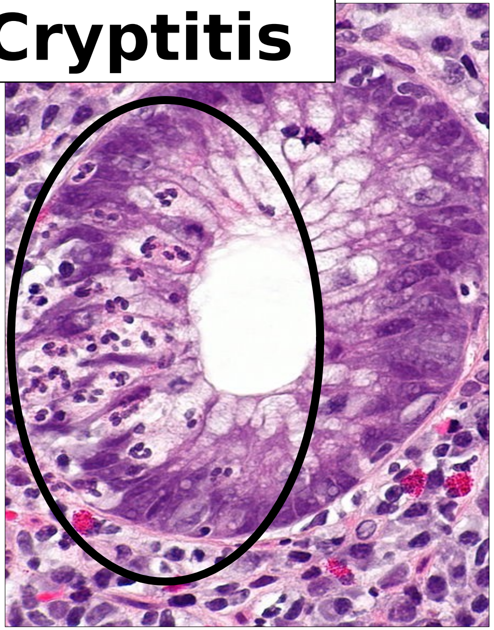
Mic:

- Ulceration
- Inflammation: **Limited to mucosa & submucosa**
- Cryptitis & crypt abscess more prominent than crohn's



Ulceration

https://img.medscape.com/thumbnail_library/ps_150521_ulcerative_colitis_800x60



Cryptitis

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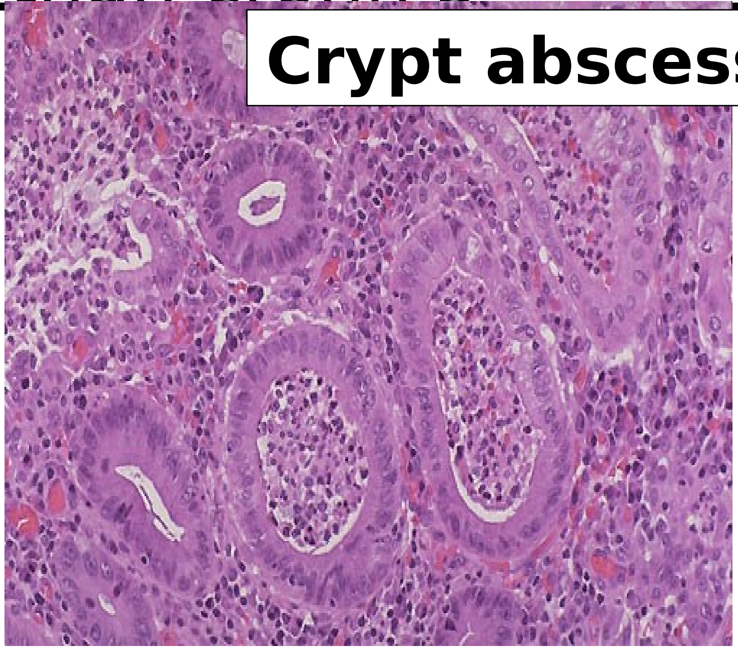
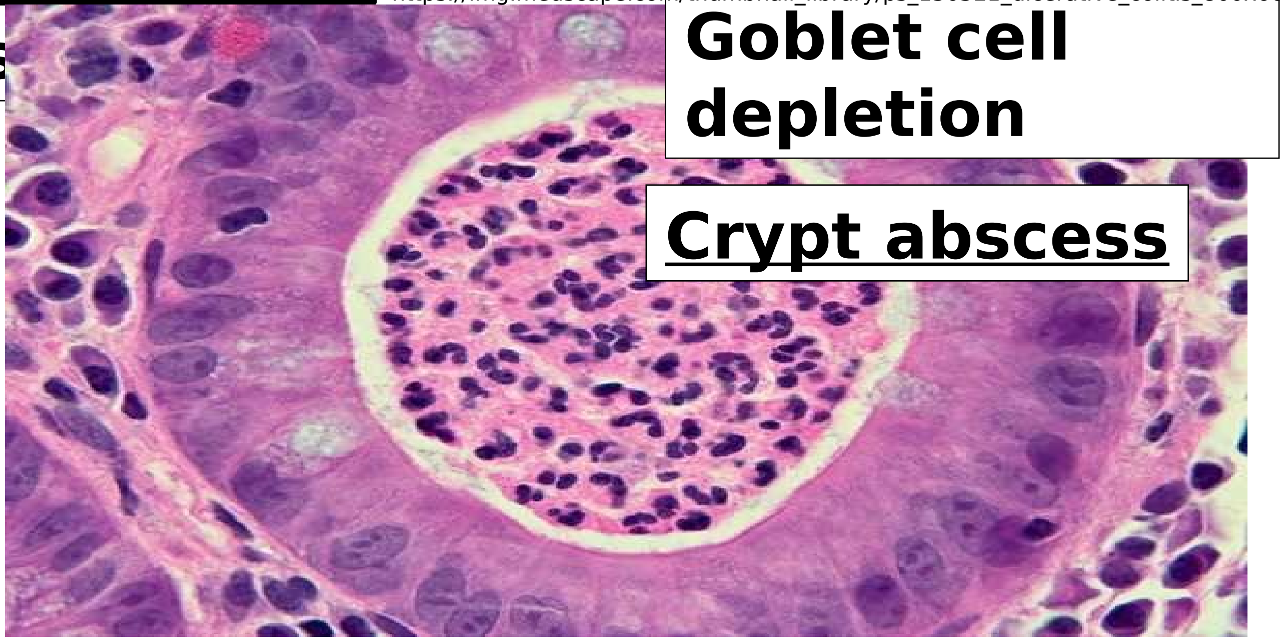


Crypt abscess

https://webpath.med.utah.edu/jpeg4/GI183.jpg



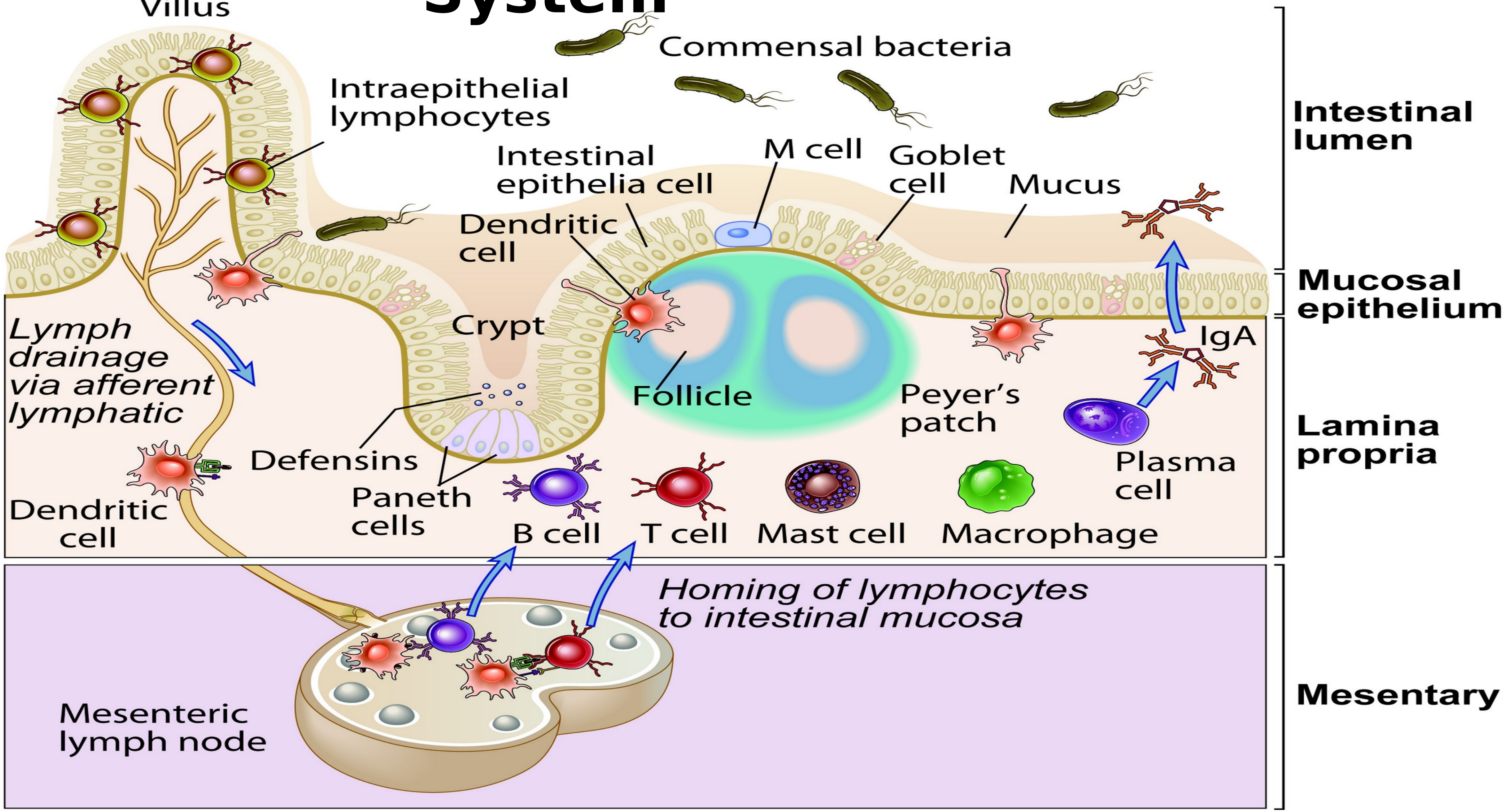
Goblet cell depletion

Crypt abscess

https://www.pathpedia.com/education/eatlas/histopathology/intestine_large/colitis_ulcerative/colitis_ulcerative_co076_1.jpeg?Width=600&Height=450&Format=4

7- What is the immunological basis of the pathological changes in descending colon?

The Gastrointestinal Immune System



Immunopathogenesis of ulcerative colitis (UC)

Is a chronic remitting inflammation most probably resulting from defects in the regulation of immune responses to commensal organisms in the gut in genetically susceptible individuals.

A. Defects in innate immunity to gut commensals.

↓ expression of defensins

⬇

↑ **commensal bacterial invasion** through the intestinal epithelium

B-Increase in proinflammatory cytokines e.g IL-1 and TNFα

Etiology

1-Upregulation of TLR4 in primary intestinal epithel

Increased LPS responsiveness

(LPS is abundantly present in the intestinal lumen as

Gram -ve bacteria account for 50% of the bacterial

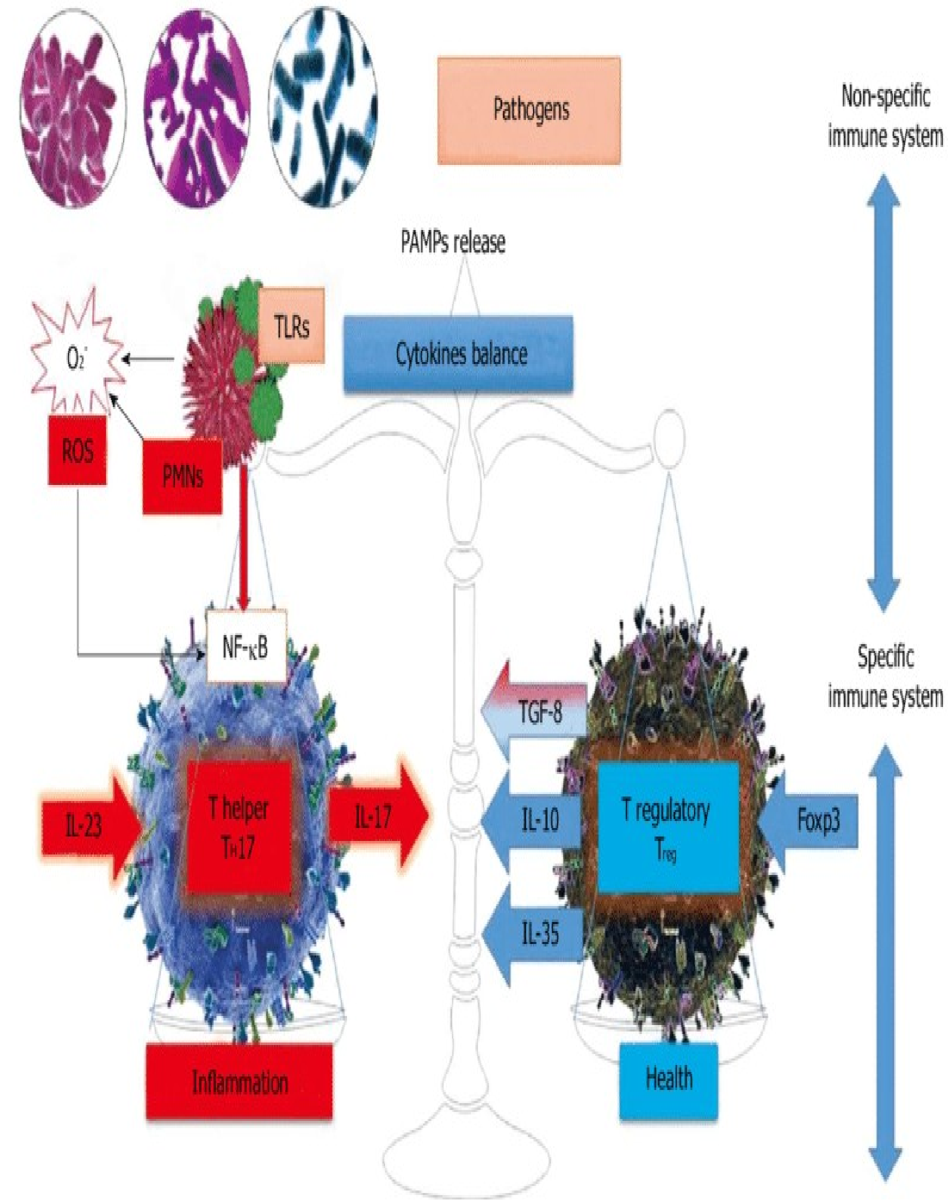
2-Increase expression of **IL-1, IL-2, IL-6, IL-12 & TNFα**

Effects

Induce intestinal macrophages, neutrophils, fibrobla

Smooth muscle cells to secrete mediators of inflamr

e.g prostaglandins, proteases & other inflammatory and

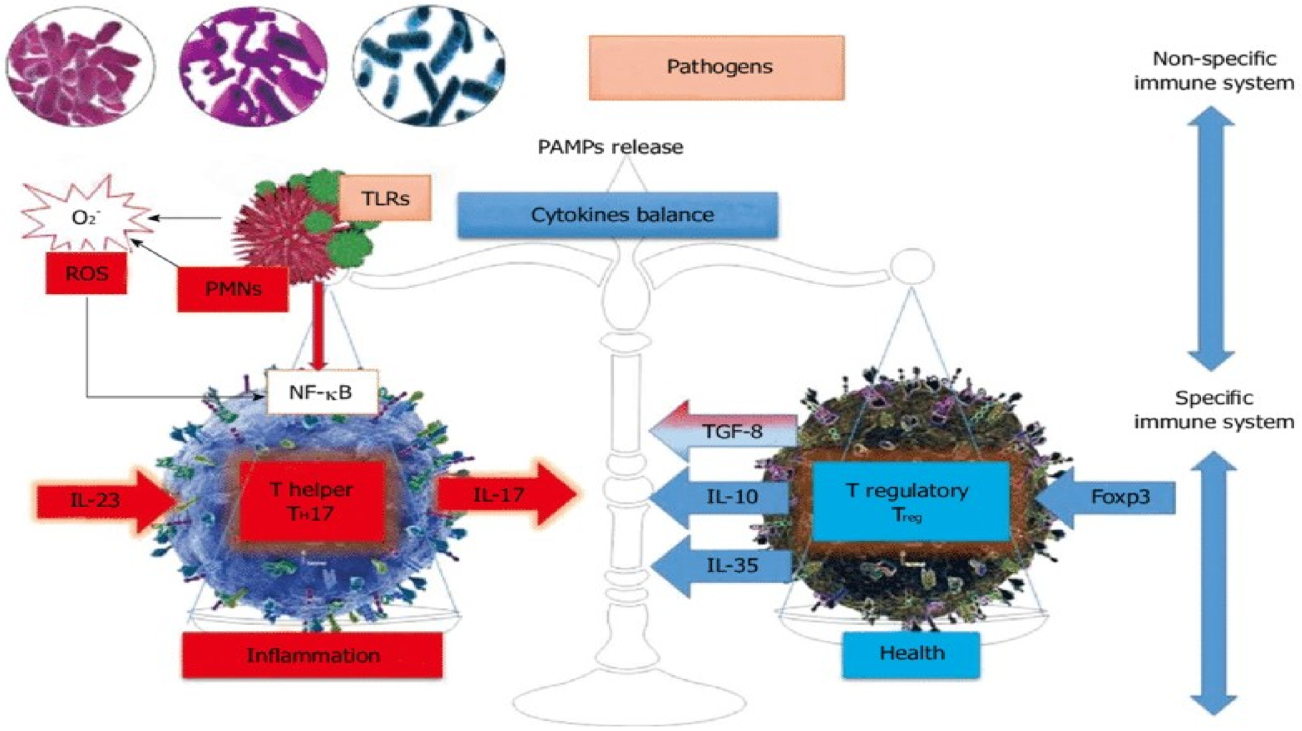


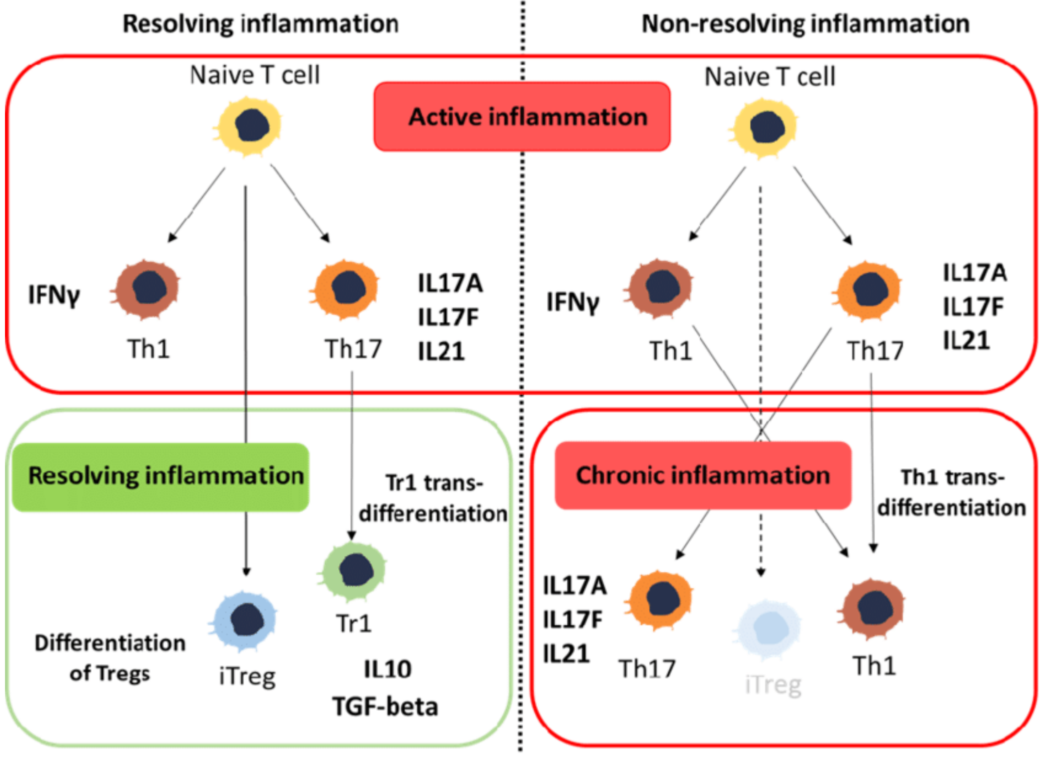
C-Abnormal Th17 response

Excess recruitment of neutrophils

D- Defective function of regulatory T cells

Inadequate suppression of immune responses to commensal





Conclusion

- Immunopathogenesis of UC in genetic susceptible humans is the **inappropriate immune responses driven by apparently normal intestinal microflora when epithelial barrier function was impaired.**
- **Breaks in this mucosal barrier** may facilitate PAMPs permeation.
- **Subsequent contact between luminal antigens& TLRs stimulates continuing immune stimulation** rather than tolerance towards luminal microflora.
- **TLRs may exert their effects through activating the NF-κB pathway**

  which is participated in secretion of proinflammatory cytokines & chemokines

  that link to the adaptive immune system.

Welcome Back

Diarrhea with Pain

The doctor discussed the **treatment strategy** with Mounir

Induction of **remission** is the primary target followed by **maintenance** therapy.

Combination of the following agents was prescribed:

- **5 ASA (oral/enema in left sided disease)**
- **Steroids (methylprednisolone , hydrocortisone, budesonide) to induce remission as the patient did respond within the first 2 weeks**

Diarrhea with Pain

Follow up

- Follow up and screening for colorectal cancer should be done

8- What is the mechanism of action of 5-Aminosalicylic acid (5-ASA)?

What is the mechanism of action of 5-Aminosalicylic acid (5-ASA)?

- **Aminosalicylates** remain **the gold standard for the ttt** of mild - moderate **Crohn‘s disease** and **ulcerative colitis**

  They acts Mainly by :

  inhibiting COX 2 inhibit synthesis of prostaglandins (eicosanoid inflammatory mediators) involved in the inflammatory process

  also inhibit synthesis of pro-inflammatory cytokines (TNF-α, IL1β, IL6)

  - They may **improve symptoms within 1 week of initiating therapy** or dosage adjustment.

What are the different drugs containing 5-Aminosalicylic acid (5-ASA)?

- **What are the different drugs containing 5-Aminosalicylic acid (5-ASA)?**

1. **Sulfasalazine**
2. **Mesalazine**
3. **Olsalazine**
4. **Balasalazide**

- **What are the difference between 5-ASA compounds ?**

For 5-ASA compounds :

Mention :

- Its routes of administration & dosage forms

- Its side effects

•What are the difference between 5-ASA compounds ?

1. Sulfasalazine: Orally.

A combination of Sulfapyridine & 5-Aminosalicylic acid□ Split in colon by bacteria into:

a) Sulfapyridine □ Absorbed □ Most of side effects as:

- Nausea, Vomiting,
- Photosensitivity And Skin Discoloration,
- Oligospermia But Reversible, which may be tolerable for most patients.
- Severe adverse reactions associated with sulfasalazine include Stevens-Johnson syndrome, agranulocytosis, crystalluria, pancreatitis, and hepatitis, which may necessitate discontinuation of therapy.

b) 5-Aminosalicylic acid □ Local anti-inflammatory□ Poorly absorbed from small intestine.

limited systemic side effects

2. Mesalazine: 5-Aminosalicylic acid. Taken **orally**. **Safer** than Sulfasalazine.

3. Olsalazine: : Two 5-Aminosalicylic acid linked together. Taken **orally**

4. Balasalazide: Prodrug of Mesalazine activated by colonic bacteria.

5-aminosalicylic acid compounds are administered: **Orally:** tablets or capsules
Rectally: suppositories, enemas or foam

- 5 -ASA is **poorly absorbed** from the GI tract and thus are considered primarily topical agents, with **limited systemic side effects and drug interactions**.
- 5 –ASA compounds are **contraindicated** in patients **with aspirin allergy or G6PD** deficiency
- BUT they appear to be **safe in pregnancy**
- Mesalamine and other 5-ASA's that **do not have a sulfa moiety fewer side effects** and are well tolerated.
- In **rare** instances, mesalamine, olsalazine, and balsalazide **have been associated with renal function impairment;** therefore, renal function should be monitored during therapy

- **What are the routes of administration of corticosteroids?**
- **When to use such routes?**

- **What are the routes of administration of corticosteroids?**

Orally, or Topical (suppositories or foam), Retention

e

Colocort™
Hydrocortisone Rectal Suspension, USP (Retention)
100 mg/60 mL
AB to CORTENEMA®
Rx only
Paddock Laboratories, Inc.
Clindamycin and Clotrimazole Vaginal Suppositories
CORTICOSTEROIDS!
Full Offering of Both Brand & Generics
MethylPREDNIsolone Tablets, USP
4 mg
SANDOZ
NDC 0037-6830-15
cortifoam®
(hydrocortisone acetate 10%)
rectal foam
Rx Only
MEDA
15 g net wt
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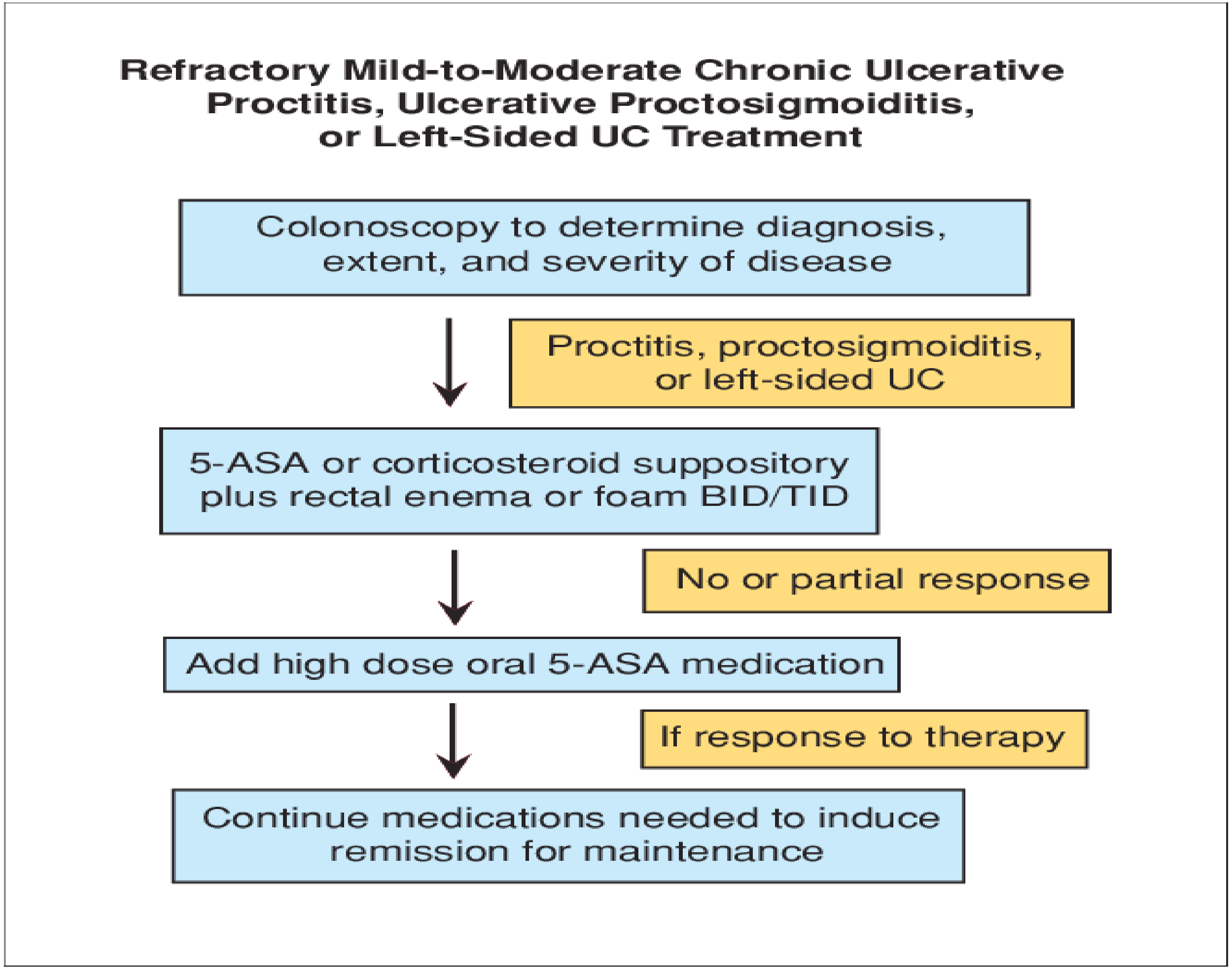
- **When to use such routes?**



Refractory Mild-to-Moderate Chronic Ulcerative Proctitis, Ulcerative Proctosigmoiditis, or Left-Sided UC Treatment

Colonoscopy to determine diagnosis, extent, and severity of disease

↓ Proctitis, proctosigmoiditis, or left-sided UC

5-ASA or corticosteroid suppository plus rectal enema or foam BID/TID

↓ No or partial response

Add high dose oral 5-ASA medication

↓ If response to therapy

Continue medications needed to induce remission for maintenance

https://www.researchgate.net/profile/Jesse_Green5/publication/51682930/figure/fig1/AS:667197613559828@1536083715899/Treatment-algorithm-for-outpatients-with-refractory-chronic-mild-to-

9- What if Mounir did not respond?

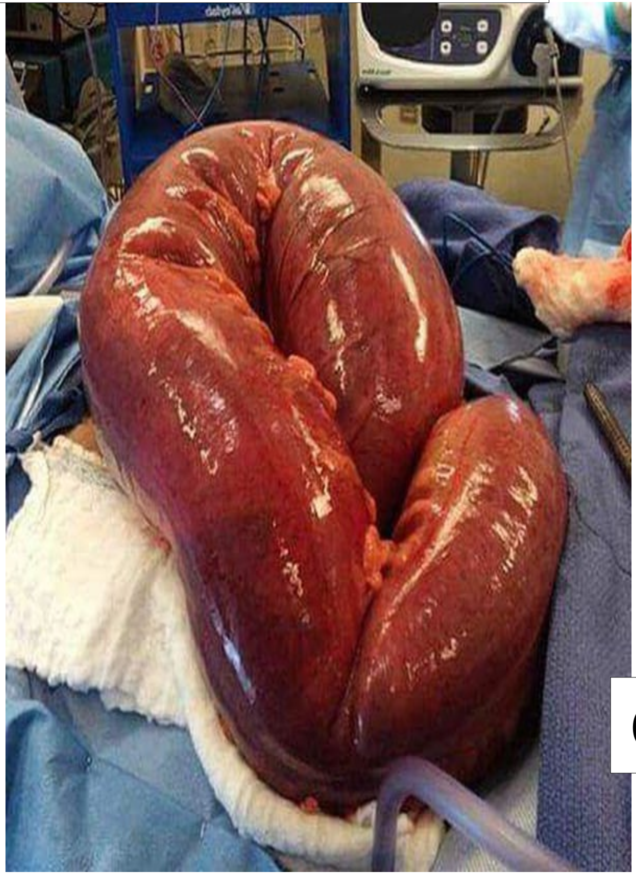
- **Immunosuppressant:** Azathioprine, and methotrexate
- **Biologic therapy:** Monoclonal Ab
  - **Anti TNF:** adalimumab, golimumab, or infliximab
  - **Integrin Antagonist** : vedolizumab
- **JAK inhibitor**: tofacitinib

10- What are the complications that could happen to Mounir if he was not properly treated?

Complications

1. Colonic bleeding
2. **Toxic megacolon**
3. Perforation
4. Carcinoma

Toxic megacolon



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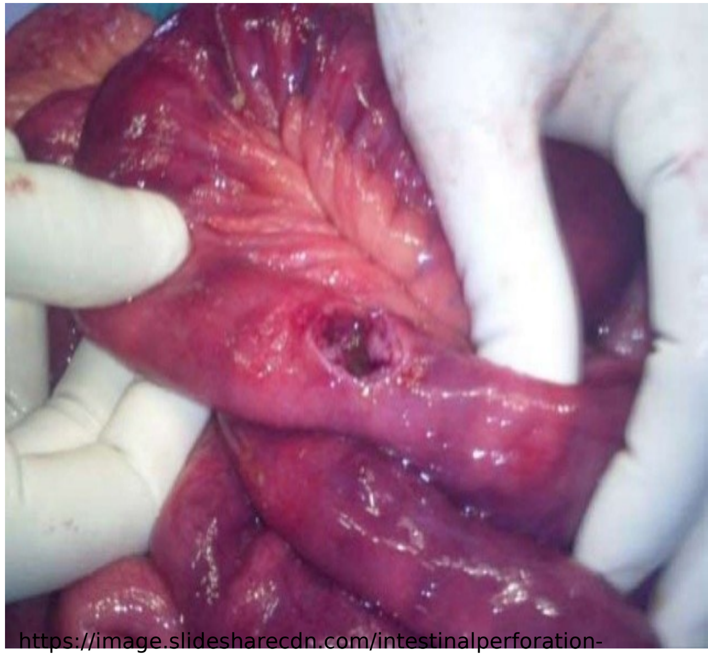
Perforation



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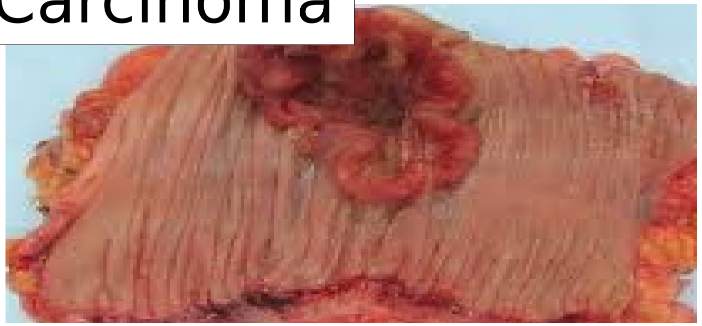
Carcinoma

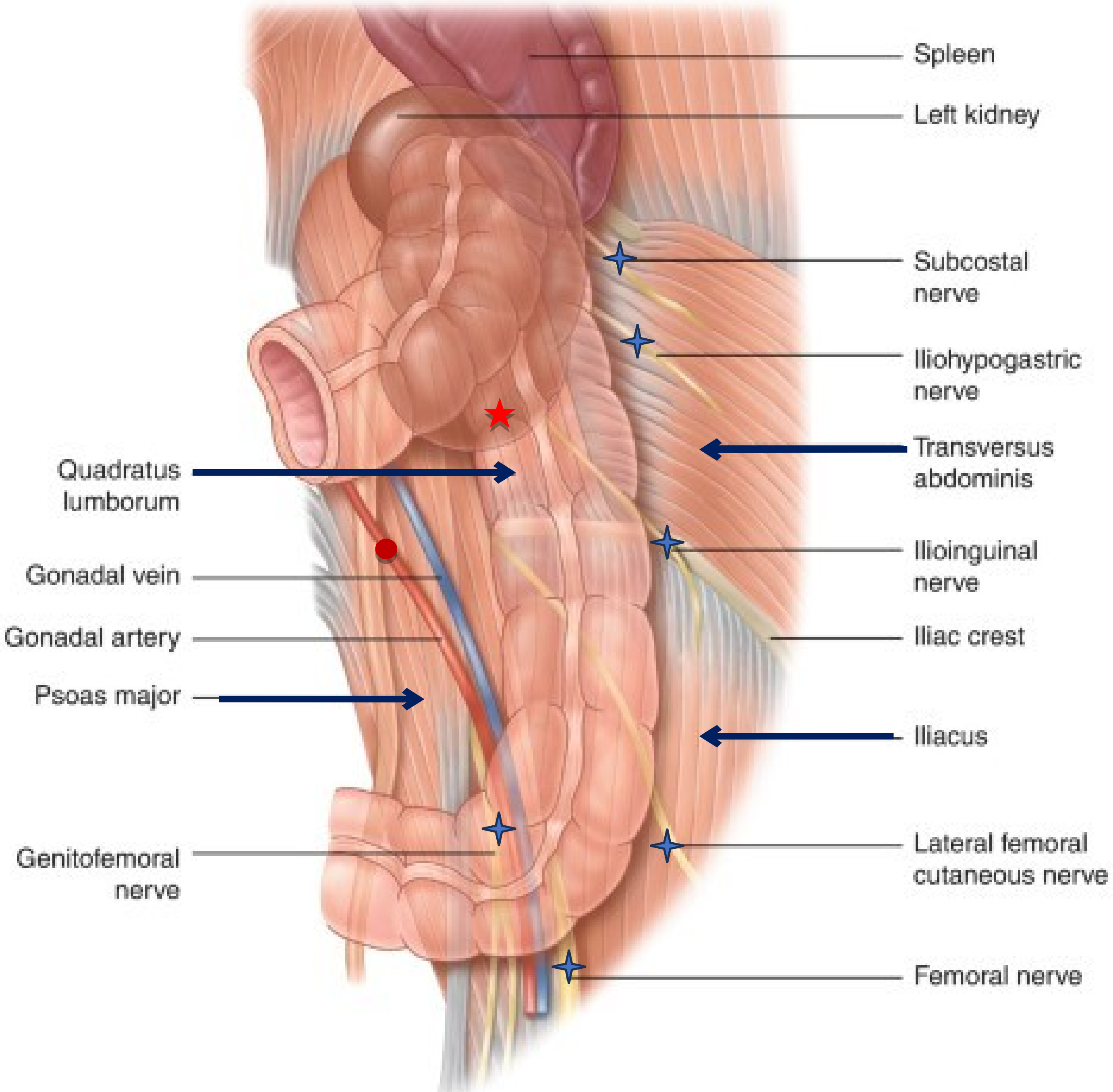


https://upload.wikimedia.org/wikipedia/commons/thumb/c/cc/Colon cancer 2.jpg/

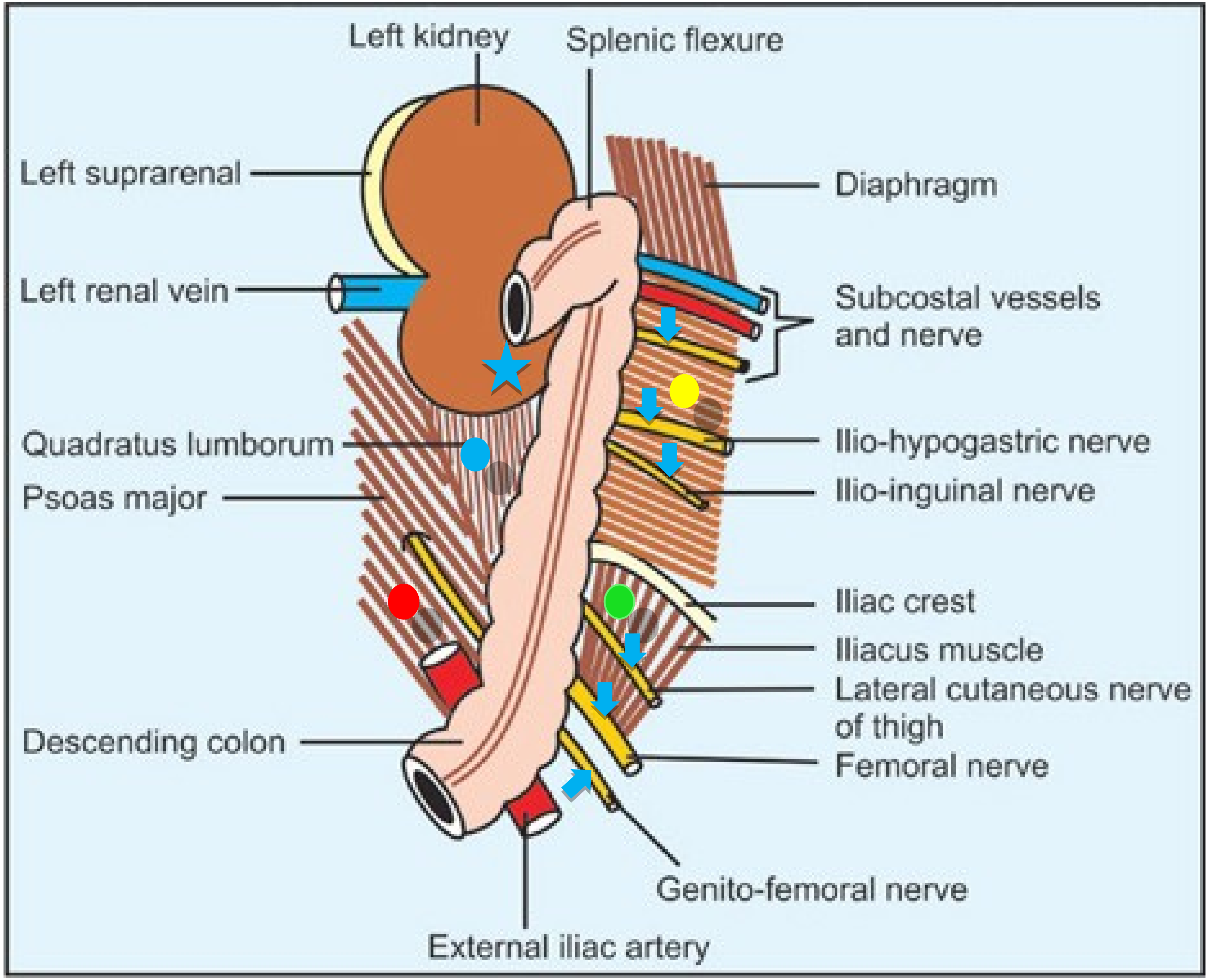
Which organ might be affected if ulcerative colitis cause posterior perforation to the wall of descending colon?

Posterior relations of descending

1. **Front of left kidney**
2. **Muscles: transversus abdominis/ Quadratus lumborum/ iliacus/ psoas major**
3. **Nerves: subcostal/ iliohypogastric/ ilioinguinal/ lat cut n of thigh/ genitofemoral/ Femoral**
4. **Vessels: left subcostal vessels, left gonadal vessels, 4th lumbar & left external**

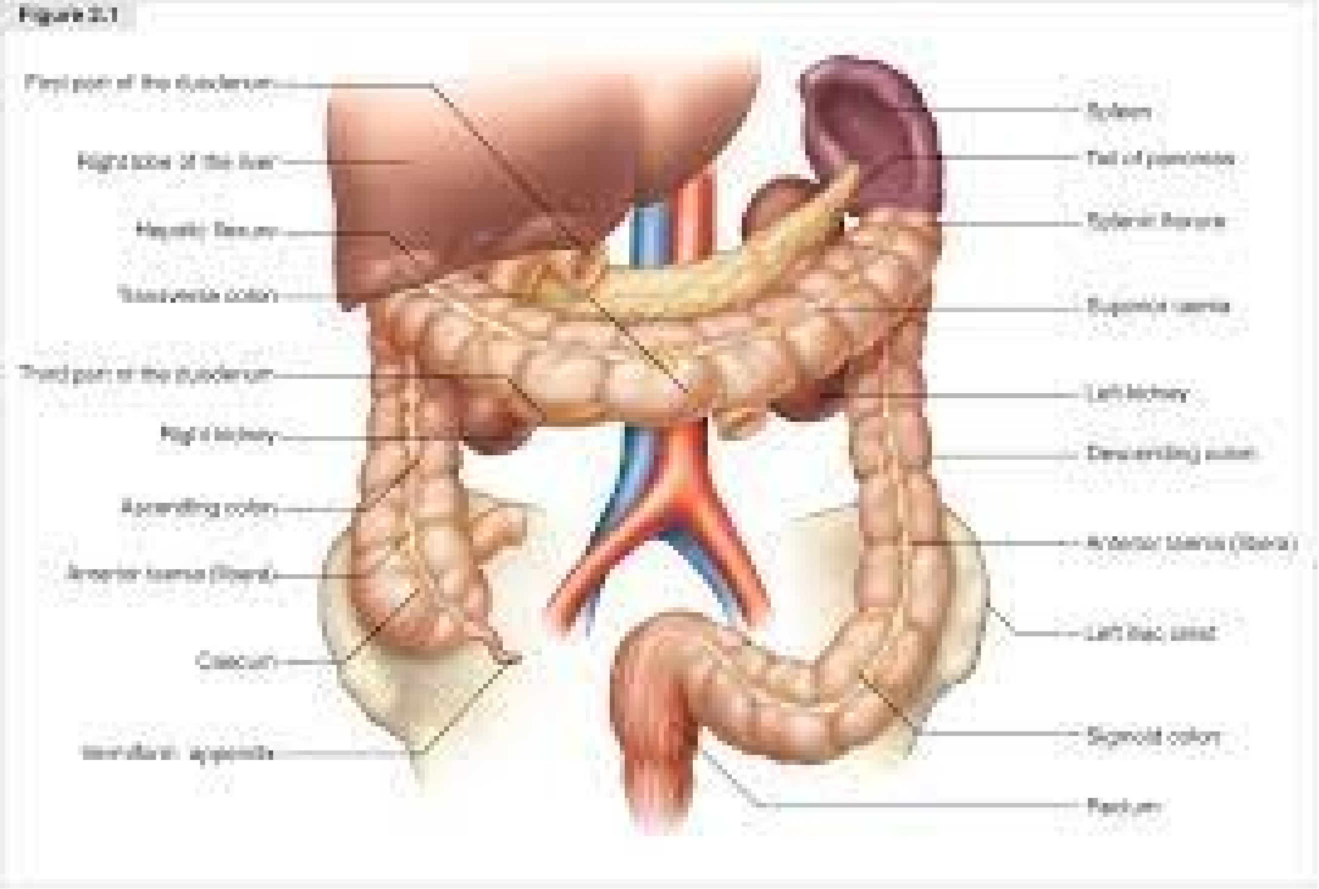


IDENTIFY Structures posterior to descendi



The organ which might be affected if ulcerative colitis cause posterior perforation to the wall of descending colon:

- **The left Kidney**



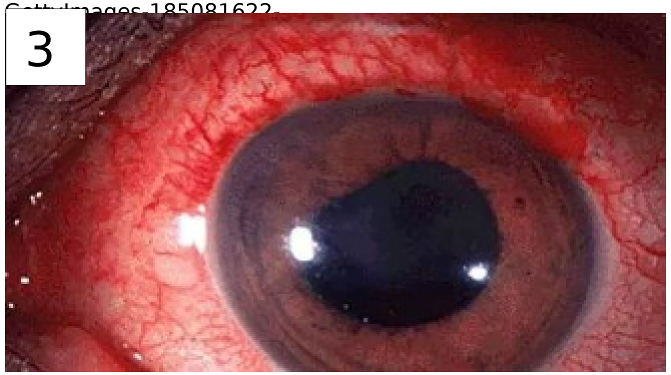
Clinical anatomy by regions, 8th edition

Extra intestinal manifestations in IBD

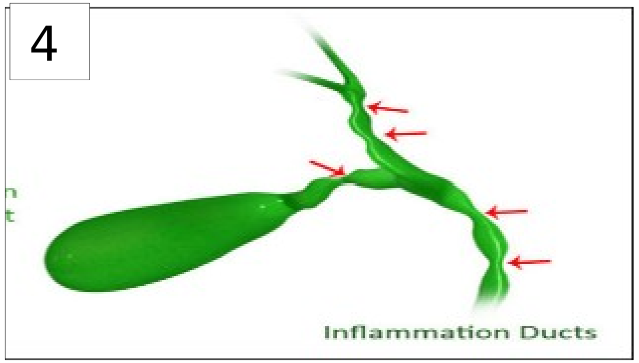
1. Migratory arthritis,
2. Ankylosing spondylitis
3. Uveitis
4. Primary sclerosing cholangitis
5. Pyoderma gangrenosa or Erythema nodusum
6. Secondary amyloidosis

https://www.verywellhealth.com/thmb/FNpkfBBh74BCL9TVg1FNeejgFr4=/768x0/filters:no_upscale():max_bytes(150000):strip_icc()/GettyImages-185081622-

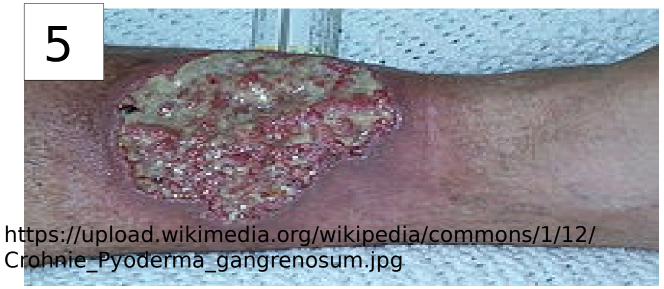
https://qualmedicaresearch.com/wp-content/uploads/2018/12/AnkylosingSpondylitis-1080x675.jpg



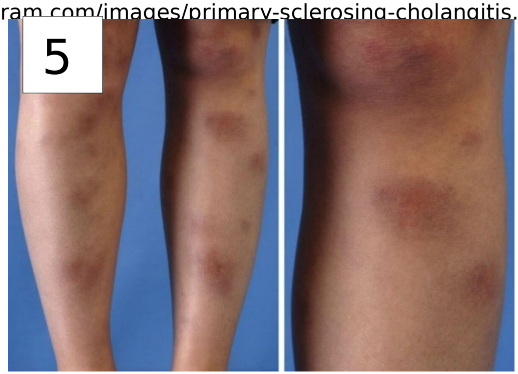
https://i0.wp.com/images-prod.healthline.com/hlcmsresource/images/galleries/uveitis/4067-Uveitis-642x361-anterior_uveitis_slide1.jpg?w=1155



http://drvikram.com/images/primary-sclerosing-cholangitis.jpg



https://upload.wikimedia.org/wikipedia/commons/1/12/Crohnie_Pyoderma_gangrenosum.jpg



Take home message

- **DD of diarrhea**

Not all diarrhea are simple infections

- ***Treat the cause***

- ***Guidelines and evidence based medicine***

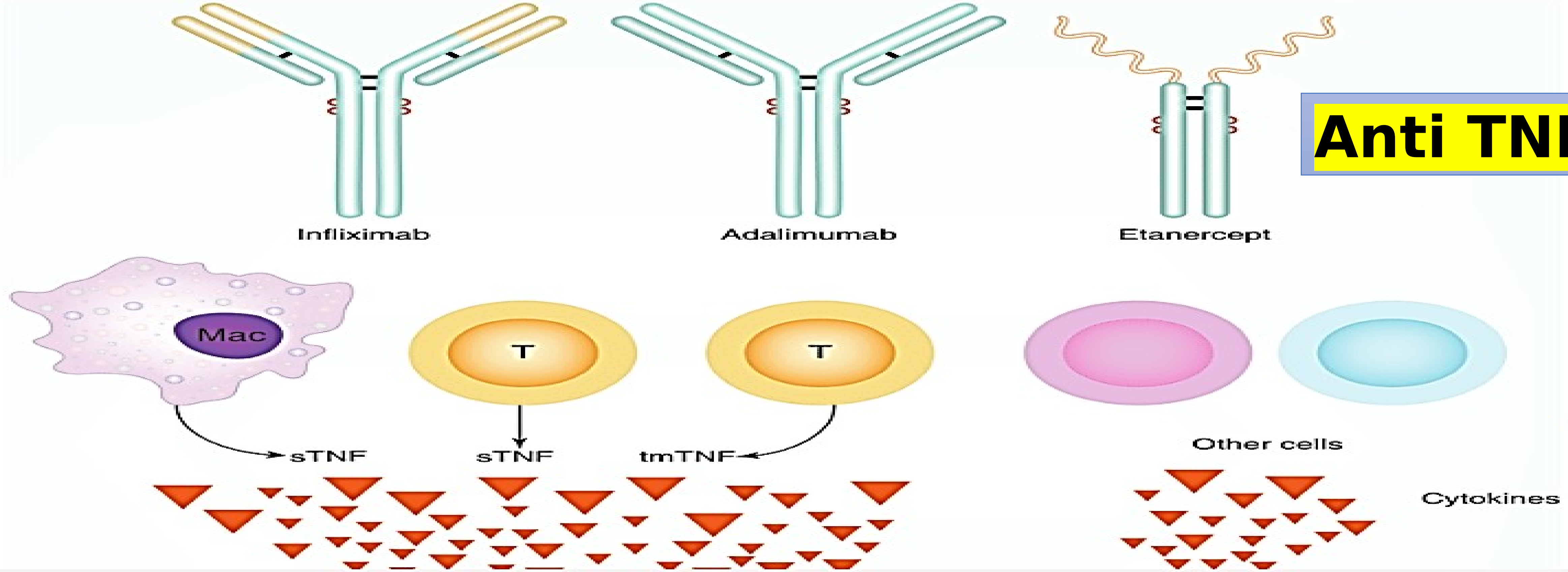
Ecco guidelines on IBD

- https://www.ecco-ibd.eu/publications/ecco-guidelines-science.html

Thank you

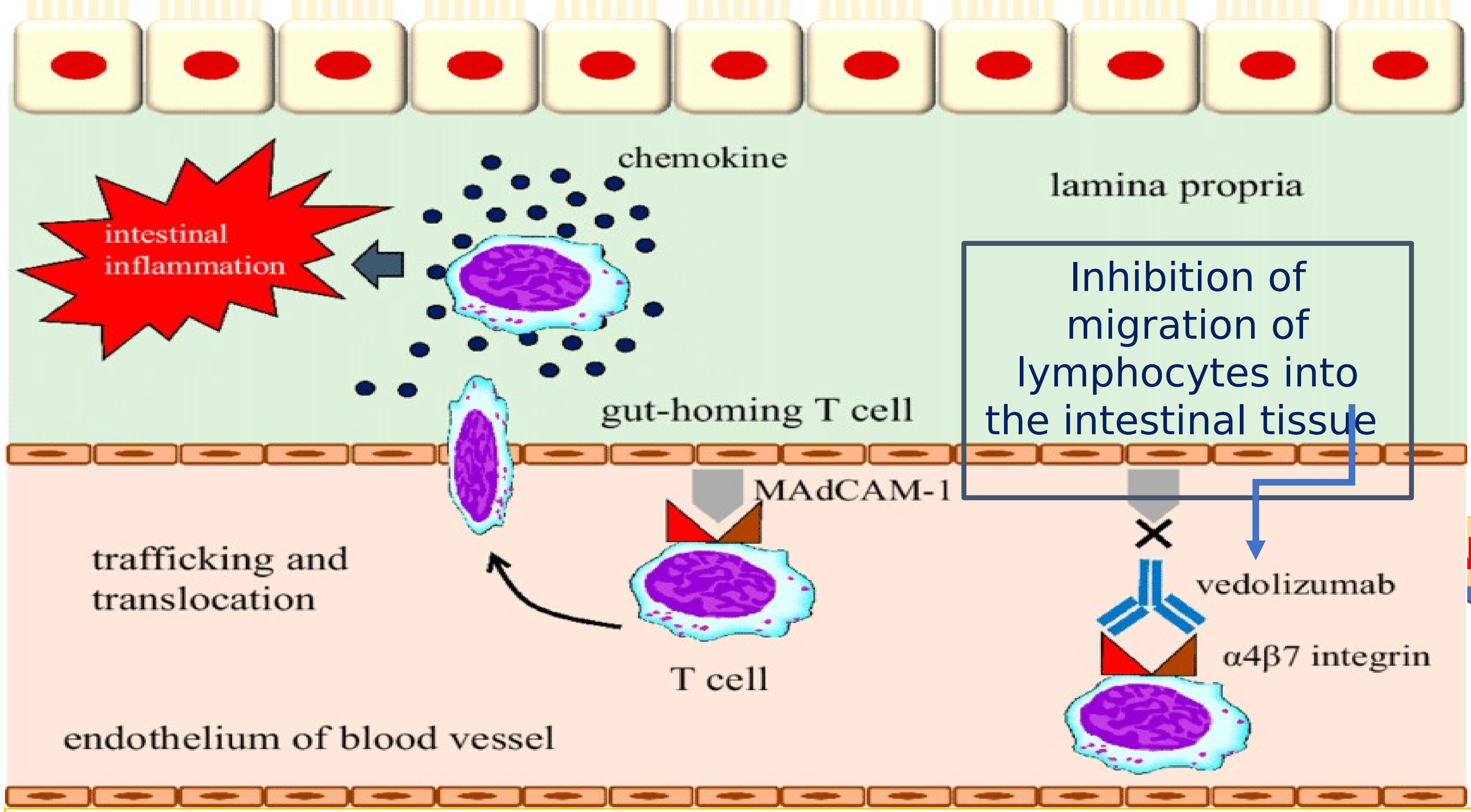
What is the mechanism of action of different preparations of biologic therapy & JAK inhibitor?

Anti TNF



- ✓ **For many years, physicians had only antitumour necrosis factor (anti-TNF) antibodies as biologicals for the treatment of IBD.**
- ✓ **In fact, anti-TNF antibodies (infliximab, etanercept) are used to diminish the increased levels of TNF-α which are increased during inflammation associated with IBD.**

Integrin Antagonist

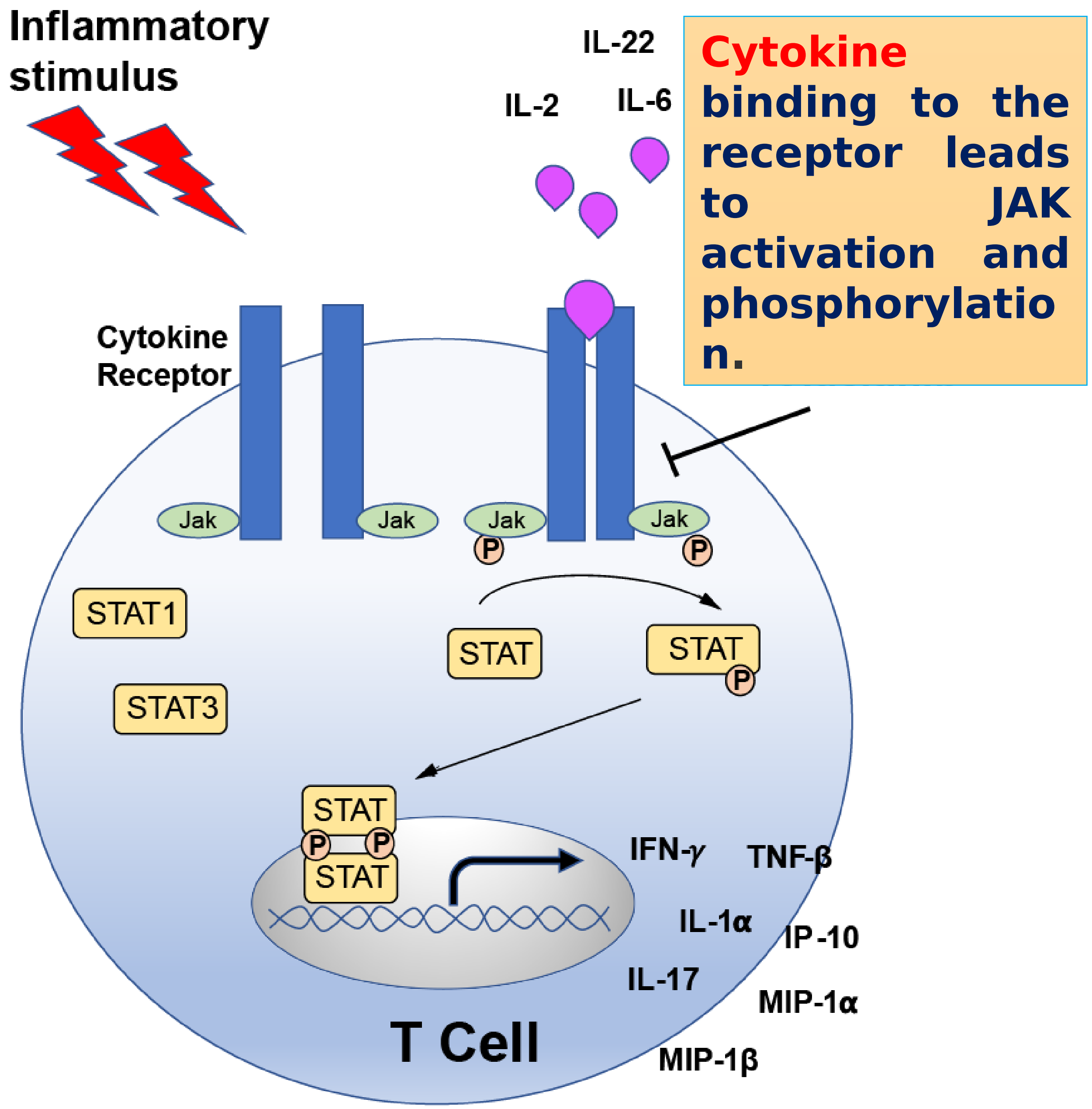


Inhibition of migration of lymphocytes into the intestinal tissue

lew Mechanism of Actio

- Vedolizumab is an **‘integrin antagonist**’ binding to **the α4β7 integrin** expressed on the surface of mononuclear cells such as t-lymphocytes.
- Circulating blood t-cells require binding of **α4β7 integrin** to mucosal address in cell adhesion molecule-1 (**MAdCAM-1**) expressed by the endothelial cells of the **GI tract** to be able to migrate into the mucosal layers.
- To prevent **the migration of inflammatory mononuclear cells into the inflamed mucosa** in patients with IBD, the integrin antagonist Vedolizumab have

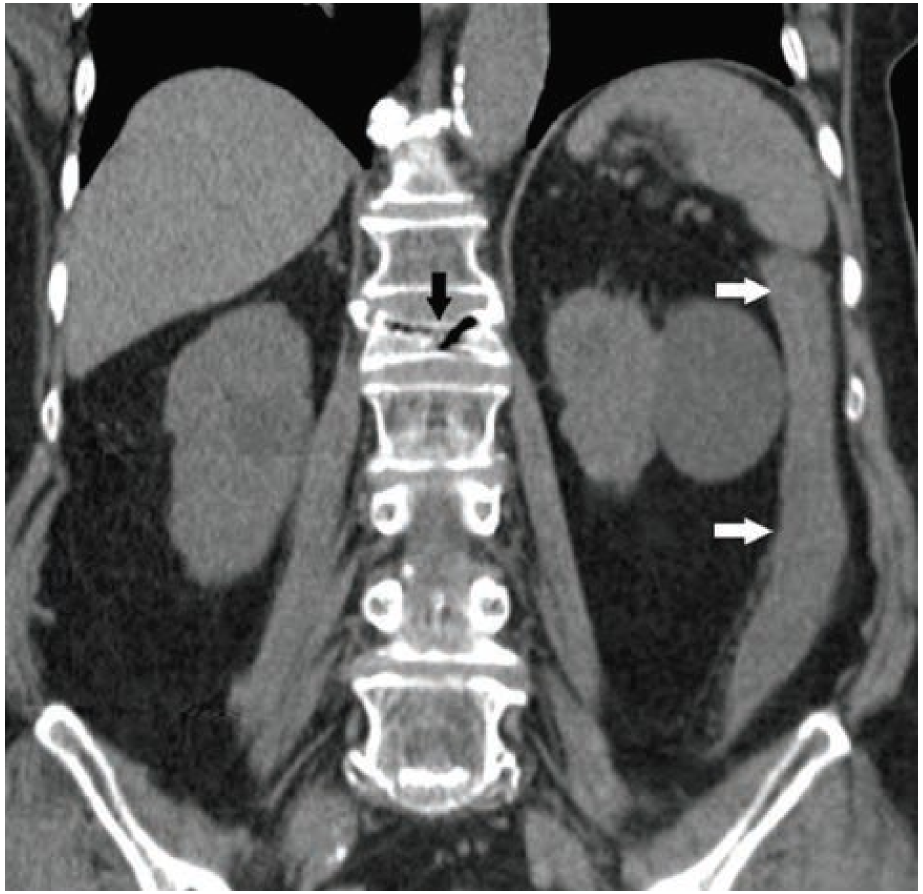
JAK Inhibitors



Cytokine binding to the receptor leads to JAK activation and phosphorylation.

- By inhibiting JAKs, tofacitinib prevents the phosphorylation and activation of STATs.
- The JAK-STAT signaling pathway is involved in the transcription of cells involved in hematopoiesis, and immune cell function.
- **Tofacitinib** works therapeutically by **inhibiting the JAK-STAT pathway to decrease the inflammatory response**.
- JAK inhibitors are **oral compounds characterized by short half-life, low antigenicity**.
- **Tofacitinib**, a pan-JAK Inhibitor (**pan= a broad inhibitory effect**), **taken orally** has shown **good efficacy and**

Diarrhea with Pain

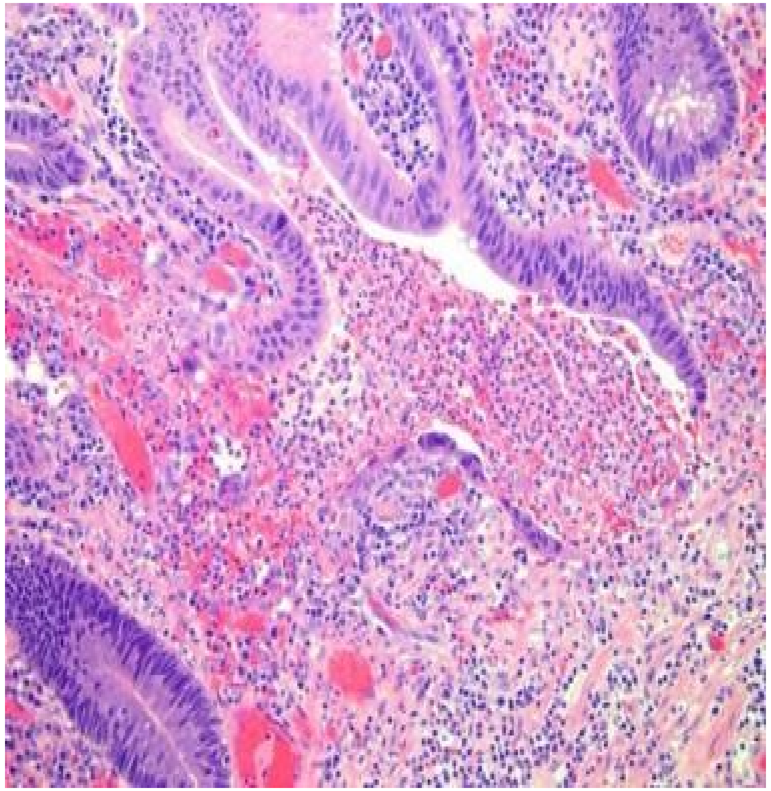


There is marked colonic wall thickening of the descending colon, with a small amount of adjacent fluid and fat stranding. The normal haustral markings of the colon have been lost (white arrows).

Diarrhea with Pain

Histopathology

Pathologic features that are typically seen include intense infiltration of the mucosa and submucosa with neutrophils and **crypt abscesses**, lamina propria with lymphoid aggregates, plasma cells, and mast cells and eosinophils, as well as **shortening and branching of the crypts (crypt distortion)** and Goblet cell depletion is also notable.



genetically susceptible individuals mount an abnormal inflammatory response to environmental triggers, such as intestinal bacteria. This leads to inflammation of the intestine with involvement of a wide array of innate and adaptive immune cell responses, with release of inflammatory mediators, including TNF-α, IL-12 and IL-23, which cause tissue damage

(1) Bacterial antigens are taken up by specialised M cells, pass between leaky epithelial cells or enter the lamina propria through ulcerated mucosa. (2) After processing, they are presented to type 1 T-helper cells by antigen presenting cells (APCs) in the lamina propria. (3) T-cell activation and differentiation results in a Th1 T cell-mediated cytokine response (4) with secretion of cytokines, including interferon gamma (IFN-γ). Further amplification of T cells perpetuates the inflammatory process with activation of non-immune cells and release of other important cytokines, including interleukin 12 (IL-12), IL-23, IL-1, IL-6 and tumour necrosis factor alpha (TNF-α). These pathways occur in all normal individuals exposed to an inflammatory insult and this is self-limiting in healthy subjects. In genetically predisposed persons, dysregulation of innate immunity may trigger inflammatory bowel disease.